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Guidelines and Criteria for the Preparation and Presentation of Complete Dossiers and of Summary Dossiers for the Inclusion of Active Substances in Annex I of Directive 91/414/EEC (Article 5.3 and 8.2)

(PLANT PROTECTION PRODUCTS)

FOREWORD

These guidelines are intended to provide guidance as to the format and presentation of the documentation to be submitted, to applicants wishing to have active substances included in Annex I to Directive 91/414/EEC, as well as to other interested parties wishing to have other information taken into account by the relevant regulatory authorities. The summaries of data and information included in the appendices to these guidelines are intended to be illustrative of the approach to be taken in the preparation of the comprehensive summaries required. The appendices concerned have not been critically examined for their technical content.

The current draft of the guidelines was prepared by the Commission with the benefit of the comments made on earlier drafts, by experts from the competent authorities of the Member States during the course of the European Commission Pilot Project meetings (ECPPM) and the first two rounds of the European Commission Co-ordination (ECCO) meetings organized by the Biologische Bundesanstalt für Land- und Forstwirtschaft (BBA) and the Pesticides Safety Directorate (PSD). In preparing this current draft, the Commission also had the benefit of the comments provided in the context of the Joint EU-OECD Meeting on guidance documents for industry data submissions (dossiers) and country data review reports (monographs), which was held in Dublin on 25 and 26 September 1997. Finally, the Commission had available to it comments provided by ECPA and by GCPF.

In preparing this draft of the guidelines, the current texts of the revised versions of the various chapters of both Annex II and Annex III of the Directive, whether existing in adopted or in draft form, were relied upon[1].

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[1] Commission Directive 93/71/EEC of 27 July 1993 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 221, 31. 8. 1993, p 27

Corrigendum to Commission Directive 93/71/EEC of 27 July 1993 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 4, 6. 1. 1996, p 16

Commission Directive 94/37/EC of 22 July 1994 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 194, 29. 7. 1994, p 65

Commission Directive 94/79/EC of 21 December 1994 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 354, 31. 12. 1994, p 16

Corrigendum to Commission Directive 94/79/EC of 21 December 1994 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 280, 23. 11. 1995, p 58

Commission Directive 95/35/EC of 14 July 1995 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 172, 22. 7. 1995, p 6

Commission Directive 95/36/EC of 14 July 1995 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 172, 22. 7. 1995, p 8

Commission Directive 96/12/EC of 8 March 1996 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 65, 15 March 1996, p 20

Commission Directive 96/46/EC of 16 July 1996 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 214, 23 August 1996, p 18

Commission Directive 96/68/EC of 21 October 1996 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. OJ No L 277, 21 October 1996, p 25

Commission Document 7109/VI/94 - rev 6, 14 July 1995 - Guideline developed within the Standing Committee on Plant Health with regard to the applicability of Good Laboratory Practice to data requirements according to Annexes II, Part A, and III, Part A, of Council Directive 91/414/EEC

Commission Document 7017/VI/95 - rev 4, 10 June 1996 - Guideline developed within the Standing Committee on Plant Health with regard to the acceptability of data, whether or not performed in accordance with the principles of Good Laboratory Practice (GLP)

Commission Document 1607/VI/97 - rev 1 of 22 July 1997 - Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market

Commission Document 7028/VI/95 - rev 2 of 6 January 1997 - Appendix A, Metabolism and distribution in plants

Commission Document 7029/VI/95 - rev 4 of 21 January 1997 - Appendix B, General Recommendations for the design, preparation and realization of residue trials

Commission Document 7524/VI/95 - rev 1 of 7 January 1997 - Appendix C, Testing of plant protection products in rotational crops

Commission Document 7525/VI/95 - rev 1 of 16 January 1997 - Appendix D, Comparability, extrapolation, group tolerances and data requirements

Commission Document 7035/VI/95 - rev 4 of 7 January 1997 - Appendix E, Processing studies

Commission Document 7030/VI/95 - rev 2 of 6 January 1997 - Appendix F, Metabolism and distribution in domestic animals

Commission Document 7031/VI/95 - rev 3 of 4 March 1996 - Appendix G, Livestock feeding studies

Commission Document 7032/VI/95 - rev 4 of 7 January 1997 - Appendix H, Storage stability of residue samples

Commission Document 7039/VI/95 - of 22 July 1997 - Appendix I, Calculation of maximum residue levels and safety intervals

Where on particular points of detail, additional or more detailed guidance is required, applicants and other interested parties are advised to contact the designated authority of the Member State to which the documentation is to be submitted. The names and addresses of the designated authorities of the Member States, the contact points in each Member State for the application of Directive 91/414/EEC, the contact points in each designated authority and in the Commission to which dossiers for new active substances should be sent and the contact points in each designated authority and the Commission to which dossiers for active substances included in the re-evaluation programme should be sent, are listed in Commission document 1606/VI/95 [2], a document which is updated on a regular basis. The requirements of the various designated authorities with respect to the number of complete and summary dossiers to be submitted for both new and existing active substances are also listed in that document.

These guidelines have been conceived as an opinion of the Commission Services and were elaborated in co-operation with the Member States. Being guidelines, they are not intended to have legally binding effects. Given its nature, this document does not prejudice any measures taken by a Member State or by the Commission in the implementation of the measures concerned, nor any case law produced by the European Court of Justice.

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2 Commission Document 1606/VI/95, rev 15 of 10 December 1997, Working document - contact points for the application of Directive 91/414/EEC, for the re-evaluation programme for existing active substances, for the evaluation of new active substances, and for the exchange of information according to Article 12

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1 GENERAL INTRODUCTION

1.1 The guidance provided and criteria specified, apply to the preparation of complete dossiers and summary dossiers, whether submitted in support of applications for inclusion of active substances in Annex I, or in the context of the review or renewal of any such inclusion.

1.2 While requiring standardization in general lay out, subject matter, terminology and units of measurement, applicants nevertheless are required to use expert judgement in preparing the documentation concerned. Within the constraints imposed by the provisions of the Directive, which require the submission of separate Annex II and Annex III dossiers, applicants nevertheless should treat these guidelines as providing a degree of flexibility.

1.3 These guidelines and criteria apply to documentation submitted for consideration, whether submitted by applicants, or by other interested parties wishing to submit technical or scientific information, with regard to the potentially dangerous effects of active substances, plant protection products, or their residues, on human or animal health or the environment.

1.4 The objective is to achieve standardization, to the extent that is practicable and feasible, of the format and presentation of documentation submitted, with a view to:

- ensuring the quality and consistency of the documentation submitted;
- facilitating efficiency and economy in the use of resources necessary for the preparation of that documentation;
- facilitating applicants in checking the completeness and quality of the documentation prior to its submission;
- facilitating the use of electronic media for the submission, archiving and retrieval of the documentation submitted; and
- facilitating efficiency and economy in the use of resources necessary for its evaluation.

1.5 Notwithstanding the clear need for evaluators, whether toxicologists, chemists or biologists, to assess original study reports and supporting data and information, summaries of the data base submitted are also required (dossier summaries), to facilitate:

- checking for completeness by applicants and by the designated authorities of the Member States;
- evaluation and assessment of the documentation concerned by the Rapporteur Member State concerned;
- evaluation and assessment of the documentation concerned by the committees established or convened by the Commission for that purpose; and
- decision making by the Commission.

1.6 Accordingly, those wishing to submit data and information in support of proposals for the inclusion of active substances in Annex I of the Directive, are themselves required to summarize, evaluate and assess the data concerned in the light of the relevant evaluative and decision making criteria. They are also required to make proposals for the decision to be made in the light of their assessment of the data and information concerned, proposals which should be supported with statements as to the rationale used.

1.7 The tiered approach specified for the preparation of dossier summaries in these guidelines is designed to facilitate efficiency in the use of evaluative resources and to facilitate decision making. The approach specified further serves to facilitate efficiency in the use of resources necessary for the preparation of summary dossiers since summaries relating to preparations, when supplemented with relevant efficacy data and information, will also be suitable for submission to the Competent Authorities of the Member States in support of applications for the authorization of the plant protection products concerned.

1.8 Forms, developed to facilitate checks to be carried out to ensure that all the necessary information, data and summaries have been included in dossiers submitted and which are to be completed and submitted by applicants, are also intended to be of benefit to applicants for the purposes of checking that all the necessary information, data and summaries have been included in dossiers being prepared for submission.

1.9 Standard Units, Terms and Abbreviations:

- Standard Units - the English language version of Standard International Units must be used in reporting and summarizing tests and studies, although other units, if desired or considered relevant, may be used in parentheses [3],

- Standard Terms and Standard Abbreviations - in the interest of avoiding confusion, standard technical terms and abbreviations as specified in Appendices 1 and 2, must be used - these Appendices will be further developed as required. Where terms and abbreviations not listed are used, a concise explanation of each such term or abbreviation should be provided in the text when it is used for the first time. In addition, a listing of all such additional terms and abbreviations should be provided as an Annex to each relevant summary document.

1.10 Hard copies of complete and summary dossiers, should be submitted. In addition, applicants should provide information in a suitable electronic form in accordance with the requirements of the relevant designated authority - applicants are advised to discuss the approach they propose using with the designated authority of the Member State to which they propose making application. A number of options are available for the electronic submission of information. Of the two options described here under, the first is the minimum considered acceptable, the second option being the preferred approach:

Option 1 the summary dossier, which contains the summary and assessment information and supporting documentation, but not the test and study reports, should be provided in a suitable word processor, and where appropriate, spreadsheet format, saved on disc;

Option 2 the entire dossier, including test and study reports, individual animal data, historical control data, other relevant data and information, as well as the summary and assessment information and supporting documentation, should be provided using the CADDY electronic dossier interchange and archiving format,

[3] Particular attention is drawn to the requirement to use metric units - *e.g.* in the case of application rates, kg active substance/ha; content of active substance in formulations, g/kg or g/l; content of residues, mg/kg; doses in feeding studies, mg/kg body weight.

which utilizes CD-ROM technology. The CADDY system allows submission of study reports as image files and has provision for the summary dossier to be included on the CD-ROM in the form of word processor/spreadsheet files, as appropriate. Further information on CADDY can be obtained from -

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and by means of the GCPF server at the following internet address -

http://www.gcpf.org/

Through the use of CADDY, savings in the costs of assembling, transporting, handling and storing complete dossiers will accrue to both applicants and the designated authorities of the Member States.

Regardless of the option chosen, applicants are encouraged, where possible, to present information in tabular form (*e.g.* GAP Tables (Documents D1 and D2), MRL lists (Documents E1 and E2), reference lists). Separate items of information such as the names of authors should be allocated to separate cell columns. A row should be allocated to each entry. Alternatively a spreadsheet format can be used. The recommended approach is intended to facilitate the subsequent manipulation of the information provided by the designated authority of the Member State to which application is made.

1.11 The requirements of the various designated authorities with respect to the number of complete and summary dossiers to be submitted for both new and existing active substances are listed in Commission document 1606/VI/95[2]. Since that document is subject to regular updating, applicants are advised to ensure that they consult the currently valid version.

2 DOCUMENTATION REQUIRED

2.1 Introduction

2.1.1 The summary documentation to be prepared and submitted, should allow a comprehensive understanding of the application and facilitate evaluation and decision making with respect to:

- the criteria specified in Articles 4 and 5 of the Directive 91/414/EEC, as appropriate;
- the criteria and guidelines for evaluation and decision making with respect to the inclusion of active substances in Annex I, where they exist; and
- to the extent that they are relevant, the evaluative and decision making criteria specified in Annex VI;

notwithstanding the clear need for reference to the individual study reports and the detailed data (*e.g.* data on relevant variables for individual animals), during the course of evaluating the data base concerned.

2.1.2 Whether the application involves a proposal for the inclusion of an active substance in Annex I, or to vary the conditions of any such inclusion, or relates to the renewal of any such inclusion, the applicant's objective should be to produce summaries and assessments which, accurately reflect the conclusions that can be derived from the data and information submitted and includes a proposal, prepared by the applicant, for the decision to be taken by the Commission on the advice of the Standing Committee on Plant Health, in accordance with Article 6 of the Directive of 1991.

2.2 Individual Documents Required

The documentation required comprises a number of separate elements and should include, in the following order:

Document A a statement of the context in which the dossier is submitted -

- first inclusion of a new active substance in Annex I,
- first inclusion of an existing active substance in Annex I,
- modification or removal of conditions or restrictions associated with the inclusion of an active substance included in Annex I,
- special review of the inclusion of an active substance in Annex I, where indications exist suggesting that the conditions of inclusion are no longer satisfied, or
- routine review anticipating expiry of the period for which the active substance was included in Annex I (*i.e.* following expiry of the period of inclusion in Annex I);

Document B where in the context of Article 8 (2) of Directive 91/414/EEC and Commission Regulations made pursuant to that Article, there is an obligation on notifiers of particular existing active substances to *take all reasonable steps to present collectively the dossiers* concerned and, where it is not possible to so present the dossiers -

- a claim that all reasonable steps were taken to present the dossiers collectively, and
- documentation to justify the claim made;

Document C where requested, copies of existing or proposed label(s) and where relevant leaflets (see Article 16 (2) of the Directive) for each of the preparations for which an Annex III dossier is submitted and in addition, labels and leaflets relevant to the uses on the basis of which import tolerances are supported or proposed. Where relevant, a translation of the texts of labels and leaflets submitted;

Document D-1 details of the intended uses (uses that are being supported by the applicant, for which data have been provided or for which data are to be provided by a specified date) and conditions of use (GAPs), on both food and feed crops and on non food and feed crops in the territory of the EU, supported in relation to the proposed inclusion of the active substance in Annex I (Document D-1) - the information concerned should be provided using forms as set out in Part 1 of Appendix 3. Uses which are not yet authorized should be identified by means of an asterisk or footnote;

Document D-2 for existing active substances, a list of current authorized uses in EU Member States and an indication of whether, or not, actually used (Document D-2) - the information concerned should be provided using forms as set out in Part 2 of Appendix 3. The listing provided should include those uses which are currently authorized but which are not being supported by the applicant. The information provided with respect to actual use, should identify those authorizations that are not currently availed of (some uses or all uses), and further should describe those instances where the rate and manner of use in practice is more restrictive than is provided for in the existing authorization (*e.g.* authorized uses of a plant protection product for which the product is not currently commercialized; uses for which the maximum authorized application rate is seldom if ever availed of);

Document D-3 details of the intended uses (uses that are being supported by the applicant, for which data have been provided or for which data are to be provided by a specified date) and conditions of use (GAPs), on both food and feed crops which are imported in significant quantities into the territory of the EU and for which import tolerances are required (Document D-3) - the information concerned should be provided using forms as set out in Part 1 of Appendix 3;

Document E-1 where they exist, a listing of EU MRLs established for the active substance, where relevant a listing of MRLs established by Member States and a listing of MRLs established by the CAC or proposed by the CCPR, together with the associated residue definitions, should be provided (Document E-1) using forms as set out in Part 3 of Appendix 3;

Document E-2 where an import tolerance is required, a listing of the MRLs established for the active substance in countries that export the plants and plant products concerned and in addition, where relevant, a listing of MRLs and import tolerances established in non-EU OECD countries, together with the associated residue definitions, should be provided (Document E-2) using forms as set out in Part 3 of Appendix 3;

Document F where relevant, in the case of existing active substances, a copy of each notification submitted to the Commission in the context of the programme of work undertaken for the examination of existing active substances pursuant to Article 8 (2) of the Directive;

Documents G - I unless a dossier in accordance with Annex II is submitted for every formulant included in the preparation (ingredient other than active substance), the following -

Document G
- a statement as to whether the substance is permitted in food, animal feeding stuffs, medicines or cosmetics in accordance with Community legislation,

Document H
- a copy of the safety data sheet prepared in accordance with Directive 67/548/EEC, and

Document I
- where requested, other available toxicological and environmental data;

Document J where relevant and desired, a statement to indicate the data and information involving industrial and commercial secrets for which confidentiality is requested, in accordance with Article 14 of Directive 91/414/EEC. To facilitate the secure handling of such information, it should be included in a separate file, where it is feasible to do so (*e.g.* details of manufacturing processes, detailed specifications of active substance and preparations and individual medical records). The file should be identified as containing industrial and commercial secrets. Where applicants wish to have data and information involving industrial and commercial secrets treated as confidential, applicants should -

- taking account of the provisions of Article 14 of Directive 91/414/EEC and of Council Directive 90/313/EEC of 7 June 1990 on the freedom of access to information on the environment, provide a listing of the data and information for which confidentiality is requested, clearly cross-referenced, for each item, to the relevant test and study reports, as well as to the dossier summaries and supporting documentation submitted - the listing should be included in the file referred to above,

- for each item listed, provide a justification for the claim that it is, or constitutes, an industrial and commercial secret - the justifications should be included in the file referred to above, and

- highlight other items of information for which confidentiality is requested, in relevant study reports, dossier summaries and supporting documentation (*e.g.* identity of test laboratories);

Document K-II individual test and study reports in accordance with the requirements specified in Annex II
Document K-III and in Annex III (Figure 1) -

- although Article 6.2 of the Directive provides that an Annex III dossier for at least one preparation be submitted, in order to ensure that the Annex I inclusion, in principle, embraces all uses that are being supported, thereby facilitating authorization of preparations containing the active substance by Member States for all such uses, the number of preparations for which an Annex III dossier is submitted should be sufficient to reflect the types of formulations and applications envisaged, as well as worst case scenarios for operator, worker and environmental exposure,

- since in accordance with Article 5.1 of Directive 91/414/EEC, it is necessary that the impact of residues, consequent on application consistent with good plant protection practice, on human and animal health be assessed, and since, it is not required that Annex III dossiers for all relevant preparations be submitted, all residue studies necessary to assess the exposure of humans and animals to residues resulting from uses which are being supported should be provided as part of the Annex II dossier, thereby facilitating the establishment or review of maximum pesticide residue levels (MRLs), as appropriate, and

- since in accordance with Article 5.1 of Directive 91/414/EEC, for the purposes of the inclusion of an active substance in Annex I, the consideration of efficacy or of unacceptable effects on plants or plant products, does not arise, Annex III dossiers submitted need not include efficacy study reports - see also subparagraph 3.1.2 (ii). However, in the case of applications for the inclusion of new active substances in Annex I, it is envisaged that an application will simultaneously be made for the authorization of a plant protection product containing the active substance. In such cases a complete overview of efficacy - to be used in the context of the consideration of the possible authorization of the plant protection product concerned, but not for the consideration of the possible inclusion of the active substance in Annex I - is required as part of the relevant Annex III dossier summary. Such overviews should be prepared in accordance with the appropriate guidelines [4].

Documents L - N a summary, evaluation and assessment of the Annex II and each Annex III dossier, prepared in accordance with the tiered structure described here under, and presented graphically in Figure 1, to include -

Document L-II *(Tier I)*
Document L-III
Document L (reference lists)

- for the individual tests and studies submitted, reports as to their quality, prepared by or on behalf of the applicant, together with a list of the test, study reports and documents submitted - see also paragraphs 3.1.1 and 3.2.1,

Document M-II *(Tier II)*
Document M-III

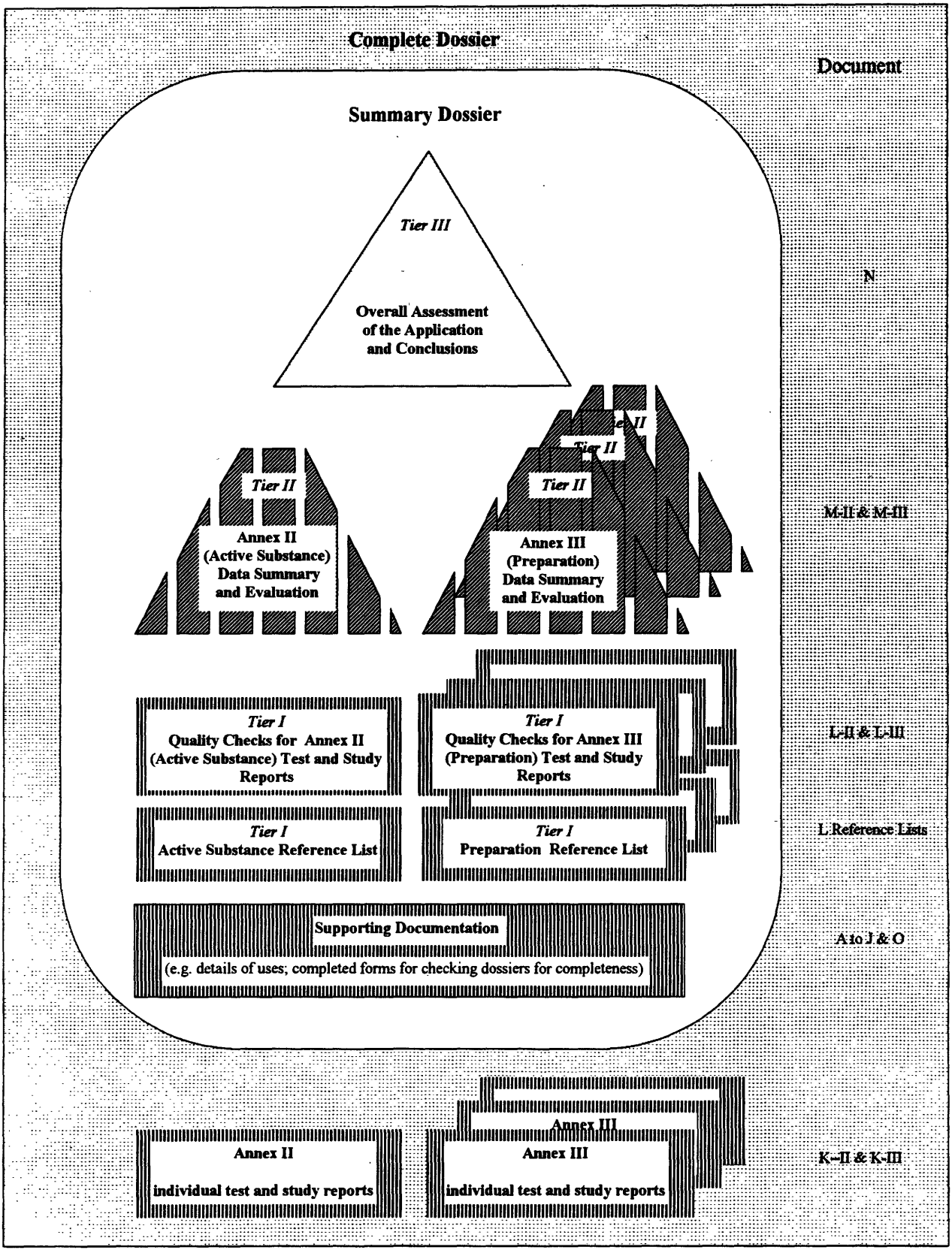
- a summary and assessment of the individual tests and studies and groups of tests and studies, as appropriate, in the light of relevant evaluative and decision making criteria - see also paragraphs 3.1.2 and 3.2.2,

- where relevant, to include an evaluation, cross referenced to the supporting documentary evidence, of the relevance of particular studies conducted regionally (*e.g.* residue data), to the agricultural, plant health and environmental (including climatic) conditions of other regions, together with the rationale for extrapolations proposed,

[4] Commission Document 7600/VI/95, rev 6 of 14 July 1997, Guidelines and criteria for the preparation and presentation of data concerning efficacy as provided in Annex III, parts A and B, section 6 of Directive 91/414/EEC concerning the placing of plant protection products on the market (biological assessment dossier)

Figure 1

DOSSIER STRUCTURE AND CONTENT



Document N *(Tier III)*

- an overall summary and assessment of the application in the light of relevant evaluative and decision making criteria, the conclusions reached by the applicant on the basis of the data and information submitted, together with a statement of the proposed conditions and restrictions to be associated with any inclusion of the active substance in Annex I, supported with the rationale for the proposals made - see also paragraphs 3.3.1 to 3.3.5, and

Document O a completed set of the forms for the checking of dossiers for completeness (evaluation forms 1, 2, 3, and 4 - see paragraphs 4.1 to 4.2.4).

2.3 Samples and Analytical Standards

Where requested, a sample of each active substance as manufactured and which complies with the specification(s) submitted, together with analytical standards for each component included in the proposed residue definition and of analytical standards for inactive isomers and impurities of toxicological or environmental concern present in significant quantities in the active substance as manufactured, should be provided.

3 DOSSIER SUMMARIES AND OVERALL ASSESSMENTS - DETAILED REQUIREMENTS

3.1 Annex II dossier

3.1.1 *Tier I* - **Document L-II - Checks as to the acceptability of the quality of individual Annex II test and study reports**

(i) The dossier summary should, in principle, include a report as to the acceptability of the quality of each individual test and study submitted to address each point of Annex II. Those reports should be assembled in six Sections as specified in subparagraph (xv). Within those Sections, or Sub-Sections, the sequence set out in the relevant part of Annex II, should be followed, ensuring that each point of Annex II is addressed.

(ii) The *Tier I* checks as to the acceptability of the quality of individual test and study reports to be submitted are intended to facilitate efficiency in the use of the resources available to the competent authorities of the Member States for the evaluation of dossiers (scientific secretariats and specialist evaluators). In particular they are intended to facilitate the checking of dossiers as to completeness and format, checks to ensure compliance with the principles of GLP/GEP, as appropriate and, checks relating to the suitability of test methods used. Except as specified hereunder for supervised residue trials and for soil dissipation studies (subparagraphs viii and ix), a summary of the findings or experimental results obtained, should not be included in *Tier I*.

(iii) In the case of testing as to the physical and chemical properties of active substances and by way of exception, it is not necessary that reports as to the quality of individual tests be provided. Details of the methodologies used should be provided in the *Tier II* summary (see paragraph 3.1.2) and instances of non compliance with or, of divergence or omissions from the requirements relating to the principles of GLP or GEP, as appropriate, should be indicated and be justified for each individual test or study.

(iv) Where the test methods used were those currently specified, and where the tests or studies concerned were conducted in accordance with the principles of GLP/GEP, as appropriate, *Tier 1* checks as to the acceptability of the quality of individual test and study reports should take the following form (examples are provided in Part 1 of Appendix 4):

1.1 the Annex II point addressed,
1.2 a description of the type of test or study;

2 reference point (location) of the report in the dossier (*e.g.* section 3, Annex IIA point 5.2.1 /01);

3.1 the names of the authors,
3.2 the title of the test or study report,
3.3 the owner of the report,
3.4 an indication as to whether it is a published or unpublished report,
3.5 the report number,
3.6 the date of the report;

4.1 the name and address of the testing facility,
4.2 the laboratory report/project number;

5 the dates of commencement and completion of experimental work;

6.1 the identity of the test substance or material (ISO common name, batch number and degree of purity),

6.2 an explicit reference to the relevant specification of composition of the test substance or material;

7.1 the identity of the test guideline used,
7.2 where test guidelines provide choice as to the method to be used, a reasoned justification for the method used,
7.3 where deviations from the test guidelines specified are employed, a description of and reasoned justification for the deviations;

8 confirmation that the principles of GLP or GEP, as appropriate, were complied with - in the event of non-compliance a description of the degree of non-compliance and a justification for non-compliance.

(v) For tests and studies for which the test methods used were not those currently specified (*i.e.* studies conducted in accordance with test guidelines which have been replaced or were never accepted), a more detailed approach is necessary in which each of the following points should be addressed in the *Tier 1* checks as to the acceptability of the quality of individual test and study reports - where a particular heading is not relevant, the reason that it is not relevant should be stated:

1.1 the Annex II point addressed,
1.2 a description of the type of test or study;

2 reference point (location) of the report in the dossier (*e.g.* section 3, Annex IIA point 5.2.2 /01);

3.1 the names of the authors,
3.2 the title of the test or study report,
3.3 the owner of the report,
3.4 an indication as to whether it is a published or unpublished report,
3.5 the report number,
3.6 the date of the report;

4.1 the name and address of the testing facility,
4.2 the laboratory report/project number;

5.1 the dates of commencement and completion of experimental work,
5.2 a statement of the objectives of the test or study;

6.1 the identity of the test substance or material (ISO common name, batch number and degree of purity),
6.2 an explicit reference to the relevant specification of composition of the test substance or material,
6.3 where available, data relevant to the storage stability of the test substance or material,
6.4 where relevant and available, data as to the stability of the test substance or material in the dosing vehicle,
6.5 where relevant and available, data as to the homogeneity of the test substance or material in the dosing or testing vehicle,
6.6 where data relating to the stability or homogeneity of the test substance is not available (*e.g.* certain older studies), a justification of the scientific validity of the study,
6.7 where relevant, information as to the physical form of the test substance or material,
6.8 full details of the composition of any dosing vehicles or solvents used;

7.1 the identity of the test method used,

7.2 where not a method specified in Annex II, a reasoned justification for the choice of method used in terms of its scientific validity and comparability with the method specified in Annex II,

7.3 on request, a copy of the method - full details of methods used which are unlikely to be accessible to competent authority of the Member State to which the dossier is submitted, should be attached to the study or test report,

7.4 where test guidelines provide choice as to the method to be used, a reasoned justification for the method used,

7.5 where deviations from the test guidelines specified, or from other methods used, are employed, a description of and reasoned justification for the deviations;

8.1 where relevant, an indication as to whether, or not, the test or study has been conducted by a laboratory certified as to its competence to conduct the test or study in compliance with the principles of GLP,

8.2 where relevant, the certifying authority,

8.3 where applicable, an indication as to whether, or not, the principles of GLP have been complied with,

8.4 where relevant, a justification for non compliance with the principles of GLP;

9.1 where relevant, a clear statement that the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC have been complied with - Good Experimental Practice (GEP),

9.2 where the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC apply, whether conducted by an official or an officially recognized testing facility or organization,

9.3 where relevant, a justification for non compliance with the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC;

10 a description of the test system;

11 the identity of any statistical and other techniques applied to the data to aid interpretation, together with adequate documentation thereof and a justification for the use of the technique selected where non standard techniques are used;

12.1 where reference to published papers is made in *Tier I* quality checks, the bibliographic references concerned,

12.2 copies of the papers concerned; and

13 where reference to unpublished data is made in *Tier I* quality checks (*e.g.* historical control data on strains of test animals) a summary of such data.

(vi) A number of specimens of *Tier I* checks as to the acceptability of the quality of individual test and study reports for Annex II studies, conducted in accordance with test guidelines other than those specified, are contained in Part 2 of Appendix 4.

(vii) It is not necessary that *Tier I* checks as to acceptability of the quality of reports be provided for reports relating to analytical methods, regardless of whether the methods concerned relate to residues analysis, analysis of active substance as manufactured or analysis of

formulations. Details of the methods of analysis concerned should be provided in the *Tier II* summary and evaluation (see paragraph 3.1.2 viii and Appendix 7, Part 2).

(viii) By way of further exception to the general rule, summaries of individual supervised residue trials submitted in accordance with Annex II, point 6.3 (*Residue trials*), rather than checks as to the acceptability of the quality of individual study reports, should be provided. For the purposes of compiling such *Tier I* summaries, the forms as contained in Part 1 of Appendix 5, should be used. Trials data relevant to all GAPs for which Community MRLs exist or are proposed, should be included. Where an import tolerance is required, trials data relevant to all GAPs for which the import tolerance is required must also be included. The forms concerned should be grouped by crops and within crops by the country in which trials were conducted.

(ix) A similar approach should be taken with respect to soil dissipation studies (Annex II, point 7.1.1.2.2. In preparing *Tier I* summaries of soil dissipation studies, the forms as contained in Part 2 of Appendix 5, should be used.

(x) The final part of *Tier I* of the summary dossier should comprise a listing of all test and study reports, test guidelines, and published papers, submitted as part of the dossier and a separate listing of all test and study reports, test guidelines, and published papers, not submitted as part of the dossier, of which the applicant is aware and which are relevant to the regulatory decision proposed (*i.e.* those that address relevant end-points). It is to be noted that applicants are obliged to submit all relevant information of which they are aware concerning potentially dangerous effects, not just a reference to such reports and papers.

(xi) In preparing the listing, applicants should conduct a detailed literature search - expert judgement is required to determine the nature and extent of the search to be conducted. The date on which the reference list was compiled, the identity of the data bases searched, the date range established for the purposes of the search (*e.g.* abstracts dated earlier than 1980 not requested), the language constraints, if any, imposed and the key words used for the purposes of the literature search, should be indicated.

(xii) The listing of test and study reports, test guidelines, and published papers submitted as part of the complete dossier, should cover each section of the dossier separately. References which relate to more than one section should be listed in each relevant section. Within sections, for each Annex II point, and where appropriate, sub-point, the list should be arranged alphabetically by author. Where for a particular author there is more than one report or paper, they should be listed in chronological order, with the most recent report or paper listed last. In cases where for a particular author, more than one reference is listed for any one year, the references should be distinguished by inserting letters after the year *i.e.* a, b, c, *etc.*, as appropriate. For each test and study report, an indication should be provided as to whether or not it is published and as to whether or not it was conducted in compliance with the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC, as appropriate. The listing of individual test and study reports should be annotated to indicate their owner and to indicate whether or not data protection is claimed in accordance with the requirements of Article 13 (3) (d) of the Directive. Before decisions to include particular active substances in Annex I are made, applicants may be required, where appropriate, to certify that the studies for which they have claimed data protection, were not submitted to the designated authorities of any of the Member States (including those of Austria, Finland and Sweden) in support of an authorization decision. A suggested format for the presentation of the listings of test and study reports, test guidelines, and published papers submitted is contained in Part 1 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xiii) A second version of the listing of test and study reports, test guidelines, and published papers, submitted as part of the complete dossier, which should again cover each section of the dossier separately, but in which the tests and studies are listed alphabetically by author and for individual authors, in chronological order, should be provided. A suggested format for the presentation of the second listing of test and study reports, test guidelines, and published papers submitted is contained in Part 2 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xiv) In the case of test and study reports and published papers not submitted, a separate listing of such documents, arranged alphabetically by author, should be provided at the end of each section. A suggested format for the presentation of the listings of test and study reports and published papers not submitted is contained in Part 3 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xv) The separate sections for which a listing of test and study reports, test guidelines, and published papers is required are as follows:

Section 1
- Identity of the active substance (Annex II, Point 1),
- Physical and chemical properties of the active substance (Annex II, Point 2),
- Further information on the active substance (Annex II, Point 3), and
- Proposals including justification for the proposals for the classification and labelling of the active substance (Annex II, Point 10);

Section 2 Analytical methods, (Annex II, Points 4.1 and 4.2);

Section 3 Toxicological and metabolism studies on the active substance (Annex II, Point 5);

Section 4 Residues in or on treated products, food or feed (Annex II, Point 6);

Section 5 Fate and behaviour in the environment (Annex II, Point 7); and

Section 6 Ecotoxicological studies on the active substance (Annex II, Point 8).

3.1.2 *Tier II* - Document M-II - Annex II dossier summary and assessment

(i) The *Tier II* summary should contain six sections such that it contains a discussion and interpretation of the results of all Annex II tests and studies and within each section, the conclusions reached. The six sections, which broadly correspond to the main headings of Annex II, are those specified in paragraph 3.1.1 (xv).

(ii) In accordance with Article 5.1 (b) of Directive 91/414/EEC, for the purposes of the inclusion of an active substance in Annex I, the consideration of efficacy or of unacceptable effects on plants or plant products, does not arise. It therefore is neither necessary nor appropriate that the *Tier II* summary include such information.

(iii) The *Tier II* summary should be confined to and rely only on that data and information contained in the Annex II dossier provided. If desired, a reference to corresponding Annex III summaries can be included.

(iv) In the case of non submission of particular studies, full justifications should be provided.

(v) Where the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC have not been followed, or where the methodologies used were not those prescribed in Annex II or, where there were deviations from the methods prescribed or other methods used, a justification of the overall quality and scientific validity of the test or study reported should be provided.

(vi) As a general rule, a concise but comprehensive summary of each individual test and study should be included. Each summary should include the following elements, as appropriate:

- the reference number of the test or study;
- the appropriate test or study reference (*e.g.* Casida *et al* 1979);
- the test guideline and method used;
- relevant GLP/GEP information;
- a brief description of the methodology used;
- a concise tabular presentation of the findings with supporting text, in which the significance of results obtained, effects and observations reported, are highlighted; and
- conclusions reached (to be highlighted);

(vii) By way of exception to the general rule, in the case of certain parts of the dossier such as that relating to the *physical and chemical properties of the active substance*, and that relating to *residue trials* (supervised residue trials) a tabular approach to the presentation of the data may be appropriate, while in the case of metabolism studies (animals, plants and soil) and soil dissipation studies, it may be more convenient to provide summaries of groups of tests and studies. In the case of supervised residues trials data, it is necessary that, where relevant, a clear statement be included to indicate the differences, if any, in the data base included in comparison to that presented by the applicant to the JMPR for the purposes of the elaboration of CAC MRLs.

(viii) Examples of parts of an Annex II *Tier II* summary are provided in Appendix 7 - Part 1 contains the suggested format for that part of a *Tier II* summary which relates to the *physical and chemical properties of the active substance*, Part 2 contains the suggested format for part of a *Tier II* summary relating to *analytical methods*, while Part 3 contains an example of part of a *Tier II* summary relating to *toxicological and metabolism studies*. Part 4 of Appendix 7 contains suggestions for the format to be used for the presentation of residue data in summary form - the suggested approach is based on that recommended in the JMPR Manual for FAO Panel Members [5]. An example of part of a *Tier II* summary relating to fate and behaviour in the environment (fate and behaviour in soil), is provided in Part 5 of Appendix 7.

(ix) For each of the six sections of the *Tier II* summary, it is particularly important that the concluding element for each point and the concluding element of sub-sections and sections, highlight the parameters of relevance to decision making, and include the rationale relied on for the conclusions reached in the light of the weight of evidence provided by the data reported.

(x) Where relevant, an evaluation, cross referenced to the supporting documentary evidence, of the relevance of particular studies conducted regionally (*e.g.* residue data), to the agricultural, plant health and environmental (including climatic) conditions of other regions, together with the rationale for extrapolations proposed, should be included.

(xi) Within each section and sub-section, having regard to the data provided, it is necessary that each decision making point be highlighted, having regard to:

- the weight of the evidence available - extent, quality and consistency of the data;
- the criteria specified in Article 5 of Directive 91/414/EEC;
- the criteria and guidelines for evaluation and decision making with respect to the inclusion of active substances in Annex I, where they exist; and
- to the extent that they are relevant, the evaluative and decision making criteria specified in Annex VI.

[5] Pesticide residues in food - 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 127.

3.2 **Annex III dossier**

3.2.1 ***Tier I* - Document L-III - Checks as to the acceptability of the quality of individual Annex III test and study reports**

(i) The dossier summary should, in principle, include a report as to the acceptability of the quality of each individual test and study submitted to address each point of Annex III. Those reports should be compiled in seven Sections as specified in subparagraph (xvi). Within those Sections, or Sub-Sections, the sequence set out in the relevant part of Annex III, should be followed, ensuring that each point of Annex III is addressed.

(ii) **Although Article 6.2 of the Directive provides that an Annex III dossier for at least one preparation be submitted, in order to ensure that the Annex I inclusion embraces all uses that are being supported, thereby facilitating authorization of preparations containing the active substance by Member States for all such uses, the number of preparations for which an Annex III dossier is submitted should be sufficient to reflect the types of formulations and applications envisaged, as well as worst case scenarios for operator, worker and environmental exposure.**

(iii) The *Tier I* checks as to the acceptability of the quality of individual test and study reports to be submitted are intended to facilitate efficiency in the use of the resources available to the competent authorities of the Member States for the evaluation of dossiers (scientific secretariats and specialist evaluators). In particular they are intended to facilitate the checking of dossiers as to completeness and format, checks to ensure compliance with the principles of GLP/GEP, as appropriate and, checks relating to the suitability of test methods used. Except as specified hereunder for supervised residue trials and for soil dissipation studies (subparagraphs ix and x), a summary of the findings or experimental results obtained, should not be included in *Tier I*.

(iv) In the case of testing as to the physical, chemical and technical properties of plant protection products and by way of exception, it is not necessary that reports as to the quality of individual tests be provided. Details of the methodologies used should be provided in the *Tier II* summary (see paragraph 3.2.2) and instances of non compliance with or, of divergence or omissions from the requirements relating to the principles of GLP or GEP, as appropriate, should be indicated and be justified for each individual test or study.

(v) Where the test methods used were those currently specified, and where the tests or studies concerned were conducted in accordance with the principles of GLP/GEP, as appropriate, *Tier I* checks as to the acceptability of the quality of individual test and study reports should take the following form (examples are provided in Part 1 of Appendix 4):

1.1 the Annex III point addressed,
1.2 a description of the type of test or study;

2 reference point (location) of the report in the dossier (*e.g.* section 3, Annex IIIA point 7.1.4 /01);

3.1 the names of the authors,
3.2 the title of the test or study report,
3.3 the owner of the report,
3.4 an indication as to whether it is a published or unpublished report,
3.5 the report number,
3.6 the date of the report;
4.1 the name and address of the testing facility,
4.2 the laboratory report/project number;

5 the dates of commencement and completion of experimental work;

6.1 the identity of the test substance or material (brand name, batch number and degree of purity),
6.2 an explicit reference to the relevant specification of composition of the test substance or material;

7.1 the identity of the test guideline used,
7.2 where test guidelines provide choice as to the method to be used, a reasoned justification for the method used;
7.3 where deviations from the test guidelines specified are employed, a description of and reasoned justification for the deviations;

8 confirmation that the principles of GLP or GEP, as appropriate, were complied with - in the event of non-compliance a description of the degree of non-compliance and a justification for non-compliance.

(vi) For tests and studies for which the test methods used were not those currently specified (*i.e.* studies conducted in accordance with test guidelines which have been replaced or were never accepted), a more detailed approach is necessary in which each of the following points should be addressed in the *Tier 1* checks as to the acceptability of the quality of individual test and study reports - where a particular heading is not relevant, the reason that it is not relevant should be stated:

1.1 the Annex III point addressed,
1.2 a description of the type of test or study;

2 reference point (location) of the report in the dossier (*e.g.* section 3, Annex IIIA, point 7.1.4 /01);

3.1 the names of the authors,
3.2 the title of the test or study report,
3.3 the owner of the report,
3.4 an indication as to whether it is a published or unpublished report,
3.5 the report number,
3.6 the date of the report;

4.1 the name and address of the testing facility,
4.2 the laboratory report/project number;

5.1 the dates of commencement and completion of experimental work,
5.2 a statement of the objectives of the test or study;

6.1 the identity of the test substance or material (brand name, batch number and degree of purity),
6.2 an explicit reference to the relevant specification of composition of the test substance or material,
6.3 where available, data relevant to the storage stability of the test substance or material,
6.4 where relevant and available, data as to the stability of the test substance or material in the dosing vehicle,
6.5 where relevant and available, data as to the homogeneity of the test substance or material in the dosing or testing vehicle,

6.6 where data relating to the stability or homogeneity of the test substance is not available (*e.g.* certain older studies), a justification of the scientific validity of the study,

6.7 where relevant, information as to the physical form of the test substance or material,

6.8 full details of the composition of any dosing vehicles or solvents used;

7.1 the identity of the test method used,

7.2 where not a method specified in Annex III, a reasoned justification for the choice of method used in terms of its scientific validity and comparability with the method specified in Annex III,

7.3 on request, a copy of the method - full details of methods used which are unlikely to be accessible to competent authority of the Member State to which the dossier is submitted, should be attached to the study or test report,

7.4 where test guidelines provide choice as to the method to be used, a reasoned justification for the method used,

7.5 where deviations from the test guidelines specified, or from other methods used, are employed, a description of and reasoned justification for the deviations;

8.1 where relevant, an indication as to whether, or not, the test or study has been conducted by a laboratory certified as to its competence to conduct the test or study in compliance with the principles of GLP,

8.2 where relevant, the certifying authority,

8.3 where applicable, an indication as to whether, or not, the principles of GLP have been complied with,

8.4 where relevant, a justification for non compliance with the principles of GLP;

9.1 where relevant, a clear statement that the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC have been complied with - Good Experimental Practice (GEP),

9.2 where the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC apply, whether conducted by an official or an officially recognized testing facility or organization,

9.3 where relevant, a justification for non compliance with the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC;

10 a description of the test system;

11 the identity of any statistical and other techniques applied to the data to aid interpretation, together with adequate documentation thereof and a justification for the use of the technique selected where non standard techniques are used;

12.1 where reference to published papers is made in *Tier I* quality checks, the bibliographic references concerned,

12.2 copies of the papers concerned; and

13 where reference to unpublished data is made in *Tier I* quality checks (*e.g.* historical control data on strains of test animals) a summary of such data.

(vii) The suggested format for the presentation of *Tier I* checks as to the acceptability of the quality of individual test and study reports for Annex III tests and studies is the same as that for Annex II tests and studies, as presented in Part 2 of Appendix 4.

(viii) It is not necessary that *Tier I* checks as to acceptability of the quality of reports be provided for reports relating to analytical methods, regardless of whether the methods concerned relate to residues analysis, or analysis of formulations.

(ix) By way of further exception to the general rule, summaries of individual supervised residue trials submitted in accordance with Annex III, point 8.1 (*Residue trials*), rather than checks as to the acceptability of the quality of individual study reports, should be provided. For the purposes of compiling such *Tier I* summaries, the forms as contained in Part 1 of Appendix 5, should be used. Trials data relevant to all GAPs for which Community MRLs exist or are proposed, should be included, except where the information concerned has already been provided as part of the relevant Annex II dossier [6]. Similarly, where an import tolerance is required, trials data relevant to all GAPs for which the import tolerance is required must be included, except where the information concerned has already been provided as part of the relevant Annex II dossier. The forms concerned should be grouped by crops and within crops by the country in which trials were conducted.

(x) A similar approach should be taken with respect to soil dissipation studies (Annex III, point 9.1.1.2). In preparing *Tier I* summaries of soil dissipation studies, the forms as contained in Part 2 of Appendix 5, should be used.

(xi) The final part of *Tier I* of the summary dossier should comprise a listing of all test and study reports, test guidelines, and published papers, submitted as part of the dossier and a separate listing of all test and study reports, test guidelines, and published papers, not submitted as part of the dossier, of which the applicant is aware and which are relevant to the regulatory decision proposed (*i.e.* those that address relevant end-points). It is to be noted that applicants are obliged to submit all relevant information of which they are aware concerning potentially dangerous effects, not just a reference to such reports and papers.

(xii) In preparing the listing, applicants should conduct a detailed literature search - expert judgement is required to determine the nature and extent of the search to be conducted. The date on which the reference list was compiled, the identity of the data bases searched, the date range established for the purposes of the search (*e.g.* abstracts dated earlier than 1980 not requested), the language constraints, if any, imposed and the key words used for the purposes of the literature search, should be indicated.

(xiii) The listing of test and study reports, test guidelines, and published papers submitted as part of the complete dossier, should cover each section of the dossier separately. References which relate to more than one section should be listed in each relevant section. Within sections, for each Annex III point, and where appropriate, sub-point, the list should be arranged alphabetically by author. Where for a particular author there is more than one report or paper, they should be listed in chronological order, with the most recent report or paper listed last. In cases where for a particular author, more than one reference is listed for any one year, the references should be distinguished by inserting letters after the year *i.e.* a, b, c, *etc.*, as appropriate. For each test and study report, an indication should be provided as to whether or not it is published and as to whether or not it was conducted in compliance with

[6] In the case of applications for the inclusion of existing active substances in Annex I, it is envisaged that residue studies relevant to all existing and proposed critical GAPs which are being supported will be provided as part of the Annex II dossier. For new active substances, the Annex II dossier will contain residue studies relevant to the critical GAPs then identified. Annex III dossiers submitted after inclusion of the active substance in Annex I, in the context of the authorization of particular preparations, should contain residue studies relevant to all additional uses proposed.

the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC, as appropriate. The listing of individual test and study reports should be annotated to indicate their owner. Before decisions to include particular active substances in Annex I are made, applicants may be required, where appropriate, to certify that the studies for which they have claimed data protection, were not submitted to the designated authorities of any of the Member States (including those of Austria, Finland and Sweden) in support of an authorization decision. A suggested format for the presentation of the listings of test and study reports, test guidelines, and published papers submitted is contained in Part 1 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xiv) A second version of the listing of test and study reports, test guidelines, and published papers, submitted as part of the complete dossier, which should again cover each section of the dossier separately, but in which the tests and studies are listed alphabetically by author and for individual authors, in chronological order, should be provided. A suggested format for the presentation of the second listing of test and study reports, test guidelines, and published papers submitted is contained in Part 2 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xv) In the case of test and study reports and published papers not submitted, a separate listing of such documents, arranged alphabetically by author, should be provided at the end of each section. A suggested format for the presentation of the listings of test and study reports and published papers not submitted is contained in Part 3 of Appendix 6. In order to facilitate the subsequent manipulation of the reference list by the designated authority to which it is submitted, the listing should be compiled using a word processing table function, using a separate row for each reference.

(xvi) The separate sections for which a listing of test and study reports, test guidelines, and published papers is required are as follows:

Section 1
- Identity of the plant protection product (Annex III, Point 1),
- Physical, chemical and technical properties of the plant protection product (Annex III, Point 2),
- Data on application (Annex III, Point 3),
- Further information on the plant protection product (Annex III, Point 4),
- Proposals including justification for the classification and labelling proposed (Annex III, Point 12.3), and
- Proposals for risk and safety phrases in accordance with Article 16(1) (g) and (h) and proposed label (Annex III, Point 12.4);

Section 2 Analytical methods (Annex III, Points 5.1 and 5.2);

Section 3 Toxicological studies (Annex III, Point 7);

Section 4 Residues in or on treated products, food or feed (Annex III, Points 8 and 12.2);

Section 5 Fate and behaviour in the environment (Annex III, Point 9); and

Section 6 Ecotoxicological studies (Annex III, Point 10).

Section 7 Efficacy data (Annex III, Point 6).

3.2.2 ***Tier II* - Document M-III - Annex III dossier summary and assessment**

(i) *Tier II* summaries should contain seven sections such that it contains a discussion and interpretation of the results of all Annex III tests and studies and within each section, the conclusions reached. The seven sections, which broadly correspond to the main headings of Annex III, are those listed in paragraph 3.2.1 (xvi).

(ii) Since in accordance with Article 5.1 (b) of Directive 91/414/EEC, for the purposes of the inclusion of an active substance in Annex I, the consideration of efficacy or of unacceptable effects on plants or plant products, does not arise, summaries of such data are not required (see also subparagraph 3.1.2 (ii)). It therefore is neither necessary or appropriate *Tier II* summaries include such information. However, where application is made for the authorization of a plant protection product, the Annex III dossier submitted must contain relevant efficacy test and study reports, summaries and overviews. In such cases, the *Tier II* summary and assessment of efficacy which should be presented as Section 7 of the *Tier II* summary and assessment, will be used by the relevant designated authority for the purposes of its examination of the application for the authorization of the plant protection product, but will not be used for the purposes of the consideration of any proposed Annex I inclusion of an active substance contained in it. *Tier II* summaries and assessments of efficacy data should be prepared in accordance with the appropriate guidelines [7].

(iii) *Tier II* summaries, which should consist of a discussion and interpretation of the results of the tests and studies contained in the Annex III dossier, for the purposes of that discussion and interpretation, should draw on data and information contained in the relevant Annex II dossier(s).

(iv) In the case of non submission of particular studies, full justifications should be provided.

(v) Where the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC have not been followed, or where the methodologies used were not those prescribed in Annex III or, where there were deviations from the methods prescribed or other methods used, a justification of the overall quality and scientific validity of the test or study reported should be provided.

[7] See footnote 4 on page 7

(vi) As a general rule, a concise but comprehensive summary of each individual test and study should be included. Each summary should include the following elements, as appropriate:

- the reference number of the test or study;
- the appropriate test or study reference (*e.g.* Casida *et al* 1979);
- the test guideline and method used;
- relevant GLP/GEP information;
- a brief description of the methodology used;
- a concise tabular presentation of the findings with supporting text in which the significance of results obtained, effects and observations reported, are highlighted; and
- conclusions reached (to be highlighted);

(vii) By way of exception to the general rule, in the case of certain parts of the dossier such as Section 1 and that relating to *residue trials* (supervised residue trials), a tabular approach to the presentation of the data may be appropriate, while in the case of metabolism studies (animals, plants and soil) and soil dissipation studies, it may be more convenient to provide summaries of groups of tests and studies. In the case of supervised residues trials data, it is necessary that, where relevant, a clear statement be included to indicate the differences, if any, in the data base included in comparison to that presented by the applicant to the JMPR for the purposes of the elaboration of CAC MRLs.

(viii) Examples of parts of an Annex III *Tier II* summary are provided in Appendix 8:

- Part 1 contains an example of that part of a *Tier II* summary which relates to *the identity of the plant protection product*; *physical, chemical and technical properties of the plant protection product*; *data on application*; and *further information on the plant protection product*;
- Part 2 contains an example of a *Tier II* summary relating to *toxicological studies*; and
- Part 3 contains an example of a *Tier II* summary relating to *ecotoxicological studies*.

(ix) The format described in Part 4 of Appendix 7 is that proposed for the presentation of residue data in summary form - the suggested approach is based on that recommended in the JMPR Manual for FAO Panel Members [8].

(x) For each of the seven Sections of the *Tier II* summary, it is particularly important that the concluding element for each point and the concluding element of sub-sections and sections, highlight the parameters of relevance to decision making, and include the rationale relied on for the conclusions reached in the light of the weight of evidence provided by the data reported.

[8] See footnote 5, page 16

(xi) Where relevant, an evaluation, cross referenced to the supporting documentary evidence, of the relevance of particular studies conducted regionally (*e.g.* rate of degradation in soil), to the agricultural, plant health and environmental (including climatic) conditions of other regions, together with the rationale for extrapolations proposed, should be included.

(xii) Within each section and sub-section, having regard to the data provided, it is necessary that each decision making point be highlighted, having regard to:

- the weight of the evidence available - extent, quality and consistency of the data;
- the criteria specified in Article 5 of Directive 91/414/EEC;
- the criteria and guidelines for evaluation and decision making with respect to the inclusion of active substances in Annex I, where they exist; and
- to the extent relevant, the evaluative and decision making criteria specified in Annex VI.

3.3 Overall Summary and Assessment (Annex II and III Dossiers) - *Tier III* - Document N

3.3.1 This, the final evaluation level, should involve an integration of the results obtained and conclusions drawn on the basis of the Annex II and Annex III tests, studies and information provided. The order in which the various elements should be presented is indicated in Table 1.

3.3.2 The *Tier III* overall summary and assessment should contain a concise summary of the data base presented in the Annex II and Annex III dossiers. That summary should be supported with a detailed statement of the applicant's overall assessment of the dossier, and should contain a reasoned statement of the conclusions which the applicant believes should be reached on the basis of the data and information provided, having regard to:

- the weight of the evidence available - the extent, quality and consistency of the data;
- the criteria specified in Article 5 of Directive 91/414/EEC;
- the criteria and guidelines for evaluation and decision making with respect to the inclusion of active substances in Annex I, where they exist; and
- to the extent that they are relevant, the evaluative and decision making criteria specified in Annex VI.

3.3.3 The *Tier III* overall summary and assessment prepared, should where relevant, include a diagrammatic representation of the metabolic pathway(s) for the active substance in animals, plants, soil and water. The molecular structure of the active substance and its metabolites, degradation and reaction products should be shown. Major pathways should be distinguishable from minor pathways, which in turn should be distinguishable from possible or suspected pathways.

3.3.4 The assessment of the data base provided, should establish the rationale for the envisaged Annex I entry. It is especially important that the overall assessment of the data base prepared include proposals relating to the conditions and restrictions to be associated with any inclusion of the active substance in Annex I, together with a detailed justification for the proposals made. A listing of all end points which are used in or are relevant to the proposed decision should be appended to the *Tier III* overall summary and assessment. In order to ensure a consistent approach in preparing the listing of end points, the format provided in Appendix 9 should be used.

3.3.5 An example of a *Tier III* summary and overall assessment for an active substance is provided in Appendix 10.

Table 1. Order in which the reasoned statement of the conclusions reached by the applicant are to be presented

Chapter	1	The active substance, its properties, uses, proposed classification and labelling
	1.1	Identity
	1.2	Physical and chemical properties
	1.3	Details of uses and further information
	1.4	Classification and labelling
Chapter	2	Methods of analysis
	2.1	for analysis of the active substance as manufactured
	2.2	for formulation analysis
	2.3	for residue analysis
Chapter	3	Impact on human and animal health
	3.1	Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products
	3.2	ADI
	3.3	ARfD (acute reference dose)
	3.4	AOEL
	3.5	Drinking water limit
	3.6	Impact on human or animal health arising from exposure to the active substance or to impurities contained in it
Chapter	4	Residues
	4.1	Definition of the residue relevant to MRLs
	4.2	Residues relevant to consumer safety
	4.3	Residues relevant to worker safety
	4.4	proposed EU MRLs and compliance with existing EU MRLs
	4.5	proposed EU import tolerances and compliance with existing EU MRLs
	4.6	basis for differences, if any, in conclusions reached having regard to established or proposed CAC MRLs
Chapter	5	Fate and behaviour in the environment
	5.1	Definition of the residue relevant to the environment
	5.2	Fate and behaviour in soil
	5.3	Fate and behaviour in water
	5.4	Fate and behaviour in air

Table 1. (Continued)

Chapter	6	Effects on non-target species
	6.1	Effects on terrestrial vertebrates
	6.2	Effects on aquatic species
	6.3	Effects on bees and other arthropod species
	6.4	Effects on earthworms and other soil macro-organisms
	6.5	Effects on soil micro-organisms
	6.6	Effects on other non-target organisms (flora and fauna)
	6.7	Effects on biological methods of sewage treatment
Final Chapter		Overall conclusions
		Proposed decision
		Further information to be submitted

4 CHECKING OF DOSSIERS FOR COMPLETENESS

4.1 Introduction

The guidance and forms provided herewith, are for use in checking dossiers for completeness, whether such dossiers are to be submitted in support of applications for inclusion of existing or new active substances in Annex I, and regardless of whether the dossiers have been submitted in the context of the review or renewal of any such inclusion. It is intended that the forms be completed by applicants and be submitted as part of the application for inclusion of an active substance in Annex I (Document O).

4.2 Suggested Approach

4.2.1 The nature and extent of the check for completeness should be such that it is confirmed that:

(i) all the required supporting documentation has been included (Documents A to J);

(ii) the Annex II and Annex III *Tier I* checks as to the acceptability of individual test and study reports, the *Tier II* dossier summaries and assessments and the *Tier III* overall summary and assessment, have been included;

(iii) all test and study reports required in accordance with the requirements of Annex II (Documents K-II) or, in the case of particular test and study reports, either a justification for non provision, or an undertaking to provide them at a future specified date, have been provided; and

(iv) all test and study reports required in accordance with the requirements of Annex III (Documents K-III) or, in the case of particular test and study reports, either a justification for non provision, or an undertaking to provide them at a future specified date, have been provided.

4.2.2 Specimen forms for use in checking dossiers for completeness are provided in Appendix 11:

Part 1 Evaluation Form 1 - for use in checking that the required supporting documentation has been provided;

Part 2 Evaluation Form 2 - for use in checking that the required Annex II and Annex III dossier summaries and an overall assessment, have been provided;

Part 3 Evaluation Form 3 - for use in checking that all test and study reports required in accordance with Annex II have been provided, and

Part 4 Evaluation Form 4 - for use in checking that all test and study reports required in accordance with Annex III have been provided.

4.2.3 A completed set of evaluation forms 1, 2, 3 and 4 (Document O - hard copy and diskette) must accompany each dossier submitted. The completed forms will be used by the competent authority of the Member State concerned in conducting its initial evaluation of the dossier to check it for completeness.

4.2.4 Although it is not necessary that completed forms be submitted, forms and supporting documentation for use in checking the acceptability of the quality of individual test and study reports, are also provided in Appendix 11 -

Part 5 Evaluation Form 5 - for use in checking that the *Tier 1* quality checks for individual test and study reports conducted in accordance with test methods other than those currently specified, are themselves of acceptable quality.

Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies, and

Part 7 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies.

APPENDIX 1

STANDARD TERMS AND ABBREVIATIONS

Part 1 Technical Terms

A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units

ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DRES	dietary risk evaluation system
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	median effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector

GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilization concentration or median inhibitory concentration [9]
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous

[9] The first time the abbreviation is used in a document, it should be defined (using a footnote to do so)

IVF	*in vitro* fertilization
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H) [9]
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC_{Lo}	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LD_{Lo}	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mole(s)
MOS	margin of safety

mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration) or number of observations [9]
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter content
op	organophosphorous pesticide
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant)

PNEC	predicted no effect concentration
po	by mouth
P_{OW}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	rotations per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square

SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TID	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low
TDR	time domain reflectrometry
TER	toxicity exposure ration
TER_I	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic carbon
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year

<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory

GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme

WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

APPENDIX 2

PREPARATION (FORMULATION) TYPES AND CODES*

Code	Description	Definition
AB	Grain bait	Special forms of bait.
AE	Aerosol dispenser	A container-held preparation which is dispersed generally by a propellant as fine droplets/particles upon actuation of a valve.
AL	Other liquids to be applied undiluted	Self defining.
BB	Block baits	Special forms of bait.
BR	Briquette	Solid block designed for controlled release of active ingredient into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CG	Encapsulated granule	A granule with a protective or release controlling coating.
CS	Capsule suspension	A stable suspension of capsules in a fluid normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous preparation to be applied as a solid dispersion after dilution in water.
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to seed.
EC	Emulsifiable concentrate	A liquid, homogenous preparation to be applied as an emulsion after dilution in water.
ED	Electrochargeable liquid	Special liquid preparation for electrostatic (electrodynamic) spraying.
EO	Emulsion, water in oil	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in water in a continuous organic liquid phase.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in an organic liquid in a continuous water phase.
FD	Smoke tin	Special form of smoke generator.

Appendix 2 **Preparation (Formulation) Types and Codes***

Code	Description	Definition
FG	Fine granule	A granule in the particle size range from 300 to 2500 μ.
FK	Smoke candle	A smoke generator in the form of a candle.
FP	Smoke cartridge	Special form of smoke generator.
FR	Smoke rodlet	Special form of smoke generator.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed either directly or after dilution.
FT	Smoke tablet	Special form of smoke generator.
FU	Smoke generator	A combustible preparation generally solid, which upon ignition releases the active substances in the form of a smoke.
FW	Smoke pellet	Special form of smoke generator.
GA	Gas	A gas packed in pressure bottle or pressure tank.
GB	Granular bait	Special forms of bait.
GE	Gas generating product	A preparation which generates a gas by chemical reaction.
GG	Macrogranule	A granule in the particle size range from 2000 to 6000 μ.
GP	Flo-dust	Very fine dustable powder for pneumatic application in glass-houses.
GR	Granule	A free-flowing solid preparation of a defined granule size range ready for use.
GS	Grease	Very viscous preparation based on oil or fat.
HN	Hot fogging concentrate	A preparation suitable for application by fogging equipment either directly or after dilution.
KN	Cold fogging concentrate	A preparation suitable for application by cold fogging equipment, either directly or after dilution.
LA	Lacquer	A solvent based film-forming preparation.
LS	Solution for seed treatment	A solution for application to the seed either directly or after dilution.
MG	Microgranule	A granule in the particle size range from 100 to 600 μ.
OF	Oil miscible flowable (=oil active substances in a miscible suspension)	A stable suspension of concentrate fluid intended for dilution in an organic liquid before use.

Appendix 2 Preparation (Formulation) Types and Codes*

Code	Description	Definition
OL	Oil miscible liquid	A liquid, homogenous preparation to be applied as a homogenous liquid after dilution in an organic liquid.
OP	Oil dispersible powder	A powder preparation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	A water based film forming preparation.
PB	Plate bait	Special forms of bait.
PC	Gel or paste concentrate	A solid preparation to be applied as a gel or a paste after dilution with water.
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter containing active substance.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A preparation designed to attract and be eaten by the target species.
SB	Scrap bait	Special forms of bait.
SC	Suspension concentrate (= flowable concentrate)	A stable suspension of active substance(s) in a fluid intended for dilution with water before use.
SE	Suspo-emulsion	A fluid, heterogeneous preparation consisting of a stable dispersion of active substance(s) in the form of solid particles and of fine globules in a continuous water phase.
SG	Water soluble granules	A preparation consisting of granules to be applied as a true solution of active substance after dissolution in water but may contain insoluble inert ingredients.
SL	Soluble concentrate	A liquid homogenous preparation to be applied as a true solution of the active substance after dilution with water.
SO	Spreading oil	A preparation designed to form a surface layer on application to water.
SP	Water soluble powder	A powder preparation to be applied as a true solution of the active substance after solution in water but which may contain insoluble inert ingredients.
SS	Water soluble powder for seed treatment	A powder to be dissolved in water before application to the seed.
SU	Ultra low volume (ULV) suspension	A suspension ready for use through ULV equipment.

Appendix 2 **Preparation (Formulation) Types and Codes***

Code	Description	Definition
TB	Tablet	Solid preparation in the form of small, flat plates for dissolution in water.
TP	Tracking powder	A rodenticidal contact preparation in powder form.
UL	Ultra low volume (ULV) liquid	A homogenous liquid ready for use through ULV equipment.
VP	Vapour releasing product	A preparation containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation rate normally is controlled by using suitable preparations and/or dispensers.
WG	Water dispersible	A preparation granule consisting of granules to be applied after disintegration and dispersion in water.
WP	Wettable powder	A powder preparation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
XX	Others	

* based upon the catalogue of Pesticide Formulation types and International Coding Systems, developed by GIFAP in co-operation with the German working group on documentation questions. (Arbeitsgruppe EDV Pflanzenschutz Versuchswesen). GIFAP Technical Monograph No 2. 1989.

APPENDIX 3 - Part 1

FORM FOR USE IN REPORTING DETAILS OF INTENDED USES (GAP INFORMATION)

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment				PHI (days)	Remarks:
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		(l)	(m)

Remarks: (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

APPENDIX 3 - PART 2

FORM FOR USE IN REPORTING AUTHORIZED USES AND ACTUAL USES

Authorized uses (crops, harmful organisms, rates of application, number of applications, timings of applications - growth stages and where appropriate, season)	Actual uses, if current practice is known to deviate from the authorized uses (crops, harmful organisms, rates of application, number of applications, timings of applications - growth stages and where appropriate, season)
Austria	
Belgium	
Denmark	
Finland	
France	
Germany	
Greece	
Ireland	
. . . . .	

APPENDIX 3 - PART 3

FORM FOR USE IN REPORTING MAXIMUM RESIDUE LIMITS (MRLs)

International Organization of Country	Commodity	MRL mg/kg	Residue Definition
EU			
EU Member State			
Other OECD Country			
Exporting Country			
CAC MRL			
Codex Proposal (indicate step)			

APPENDIX 4

FORMAT FOR COMPILATION OF *Tier I* QUALITY CHECKS

PART 1

SUMMARY REPORT - APPROPRIATE FOR STUDIES CONDUCTED IN ACCORDANCE WITH THE TEST GUIDELINES CURRENTLY SPECIFIED

EXAMPLE 1

1.	**Annex point(s)**	**IIA, 5.2.2 Acute toxicity - dermal**
2.	**Reference point (location) in dossier**	Volume 7, Section 3, Annex IIA, point 5.2.2 / 01
3.	**Authors (year)** **Title** **Owner, Date**	F. Keller (1991c) XXXX - Study of acute dermal toxicity in the rat. Organics Inc, unpublished report No. 20417, July 05, 1991 (c)
4.	**Testing facility**	Organics Inc, Institute of Toxicology, Castlebar, Ireland, Report 10564
5.	**Dates of work**	October 28, 1990 - December 4, 1990
6.	**Test substance**	ISO common name: XXXX, Batch number: 17002/90, Purity: 93.6 %, Specification number 4 (Document J)
7.	**Test method**	OECD 402 ≅ FIFRA § 81-2 ≅ EEC B.3 Deviations - analytical confirmation of the composition of the formulation was not available at the start of the study.
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)

EXAMPLE 2

1.	**Annex point(s)**	**IIA, 5.2.3 Acute toxicity - inhalation**
2.	**Reference point (location) in dossier**	Volume 7, Section 3, Annex IIA, point 5.2.3 / 04
3.	**Authors (year)** **Title** **Owner, Date**	J. Parker (1990) XXXX - Study of acute inhalation toxicity in the rat. Organics Inc, unpublished report No. 19806, December 12, 1990
4.	**Testing facility**	Organics Inc, Institute of Toxicology, Castlebar, Ireland, Report 9,703
5.	**Dates of work**	May 29, 1990 to June 19, 1990
6.	**Test substance**	ISO common name: XXXX, Batch number: 17002/90, Purity: 94.6 %, Specification number 4 (Document J)
7.	**Test method**	OECD 403 ≅ EEC B.2 Deviations - Statistics: A.P. Rosiello, J.M. Essigmann and G.N. Wogan (1977), modified by Pauluhn (1983), based on the C.I. Bliss Maximum Likelihood method (1938)
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)Glasnevin, Dublin 7, Ireland)

EXAMPLE 3

1.	**Annex point(s)**	**IIA, 5.3.2 Subchronic toxicity in rats**
2.	**Reference point (location) in dossier**	Volume 8, Section 3, Annex IIA, point 5.3.2 / 02
3.	**Authors (year)** **Title** **Owner, Date**	R. Eiben, E. Hartmann (1992) XXXX - Subchronic toxicity study in wistar rats (thirteen-week administration in the diet with a four-week recovery period). Organics Inc, unpublished report No. 21627, August 18, 1992
4.	**Testing facility**	Organics Inc, Institute of Toxicology, Castlebar, Ireland, Report No 11,204
5.	**Dates of work**	October 10, 1990 - February 04, 1991
6.	**Test substance**	ISO common name: XXXX, Batch number: 17002/90, Purity: 93.6 %, Specification number 4 (Document J)
7.	**Test method**	OECD 408 ≅ FIFRA § 83-1 ≅ EEC Directive 88/302/EEC, OJ No L 133 of 30 May 1988 Deviations - none
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)

EXAMPLE 4

1.	**Annex point(s)**	**IIA, 5.3.2 Subchronic toxicity - dog**
2.	**Reference point (location) in dossier**	Volume 9, Section 3, Annex IIA, point 5.3.2 / 04
3.	**Authors (year)** **Title** **Owner, Date**	R. D. Jones, L. E. Elcock (1994) XXXX: 13-Week subchronic feeding study in beagle dogs. Organics Inc, unpublished report No. MR7442, December 07, 1994
4.	**Testing facility**	Organics Inc, Institute of Toxicology, Castlebar, Ireland, Report No 13,256
5.	**Dates of work**	November 05, 1991 - February 06, 1992
6.	**Test substance**	ISO common name: XXXX, Batch number: 17002/90, Purity: 93.5 % - 94.9 %, Specification number 4 (Document J)
7.	**Test method**	FIFRA § 82-1 ≅ OECD 409 ≅ EEC Directive 88/302/EEC, Part B, OJ No L 133 of 30 May 1988 Deviations - none
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)

EXAMPLE 5

1.	**Annex point(s)**	**IIA, 8.1.2 Short term toxicity to birds**
2.	**Reference point (location) in dossier**	Volume 24, Section 6, Annex IIA, point 8.1.2 / 03
3.	**Authors (year)** **Title** **Owner, Date**	R. Grandy (1995) XXXX techn. - 5-day dietary LC_{50} to mallard duck. Organics Inc, unpublished report No. GMU/VE-006, April 5, 1995
4.	**Testing facility**	Organics Inc, Institute for Environmental Research, Goresbridge, County Kilkenny, Ireland, Report 24,123
5.	**Dates of work**	May 12 - 20, 1994
6.	**Test substance**	ISO common name: XXXX, Batch No. 898114002, Purity: 96.6 %, Specification number 3 (Document J)
7.	**Test method**	OECD 205 ≅ EPA 71-2 Deviations - none
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)

EXAMPLE 6

1.	**Annex point(s)**	**IIA, 8.5 Effects on soil non-target micro-organisms**
2.	**Reference point (location) in dossier**	Volume 27, Section 6, Annex IIA, point 8.5 / 03
3.	**Authors (year)** **Title** **Owner, Date**	J. Nielson (1993) Influence of XXXX SC 400 on microbial nitrogen mineralization in soil. Organics Inc, unpublished report No. AJO/113193, December 13, 1993
4.	**Testing facility**	Organics Inc, Institute for Environmental Research, Goresbridge, County Kilkenny, Ireland, Report 23,123
5.	**Dates of work**	September 13, 1993 to November 9, 1993
6.	**Test substance**	XXXX SC 400, Batch 089A from 04023/0021, contents 424.0 g as/l, Specification number 3 (Document J)
7.	**Test method**	1. Guidelines for the Official Testing of Plant Protectants, Part VI, 1-1 "Influence on the Activity of the Soil Microflora", BBA Braunschweig, Germany, March 1990 (2nd ed.). 2. ISO/DIS 1036-6: 1992, Soil Quality - Sampling - Part 6: Guidance on the Collection, Handling and Storage of Soil for the Assessment of Aerobic Microbial Processes in the Laboratory Deviations - none
8.	**GLP**	Yes (laboratory certified by the Irish Laboratory Accreditation Board, Glasnevin, Dublin 7, Ireland)

PART 2

DETAILED REPORT - APPROPRIATE FOR STUDIES NOT CONDUCTED IN ACCORDANCE WITH THE TEST GUIDELINES CURRENTLY SPECIFIED

EXAMPLE 1

Annex II A	Point addressed 5.2.2	Acute toxicity - percutaneous

Note: The report contains data on acute toxicity using different routes of application. In the dossier it is filed in each relevant section - 5.2.1 (oral toxicity); 5.2.1 (dermal toxicity); 5.2.3 (inhalation toxicity); 5.2.4 (skin irritation); 5.2.5 (eye irritation); 5.2.7 (subcutaneous toxicity); 5.2.8 (intraperitoneal toxicity).

2 Reference point: Volume 7, Section 3, Annex IIA, 5.2.2 / 03

3.1 Authors: Report: X. Xxxxxxx, X. Xxxxxxxxxxxx
Summary: X. Xxxxxxxxxxx

3.2 Title: XXX 1111 - Acute Toxicity Studies

3.3 Owner: xxxxxxxx

3.4 Published: no

3.5 Report No: xxxxx file No.: 0000

3.6 Date of report: January 7, 1980

4.1 Testing facility: Xxxxxxxxx, Xxxxxxxxxxxx, Xxxxxxxxxxxxxx, Xxxxxxxxx

4.2 Lab. report No: xxxxxxxx

5.1 Dates of experimental work: February 1979 - August 1979

5.2 Objectives: Investigation of acute dermal toxicity in rats

6.1 Test substance: XXX 1111, active substance as manufactured, 97.5 % pure, batch number: xxx

6.2 Specification: as given in document J - specification number 5

6.3 Storage stability: not applicable (single treatment only)

6.4 Stability in vehicle: not applicable

6.5 Homogeneity in vehicle: not applicable

6.6 Validity: not applicable

6.7 Physical form: oily, viscous mass with crystalline parts

6.8 Vehicle/solvent: none (undiluted application)

7.1 Test method: In house method according to the method of Noakes and Sanderson, 1969. At the time the study was performed, no particular method was compulsory. For details on the method used see description below.

7.2 Justification: The experiment was performed and complied to a great extent to then in force EPA Guidelines (Proposed Guidelines for Registering Pesticides in the US, Federal Register, Vol 43, No. 163, August 22, 1978). The method used differs from the prescribed method (EEC B.3) in the following respects ...., differences which do not compromise the scientific validity of the results obtained.

7.3 Copy of method: a description of method is included in study report

7.4 Choice of method: not applicable

7.5 Deviations: see details below

8.1 Certified laboratory: not applicable

8.2 Certifying authority: not applicable

8.3 GLP: no

8.4 Justification: When the study was performed, GLP was not compulsory.

9.1 GEP: not applicable

9.2 Type of Facility (official or officially recognized): not applicable

9.3 Justification: not applicable

Example 1 Acute toxicity - percutaneous

10 Test system -	**Animal species:**	Wistar rat (TNO/W 74)
	Source:	Winkelmann, Borchen, Germany
	Number of animals:	10 male, 15 female (5 / 10 per group)
	Dosage:	2500 and 5000 mg/kg bw
	Administration:	dermal over 24 hours - removal of the compound from the skin with lukewarm tap water and soap.
	General observations:	After administration, all animals were kept under observation for 14 days.
	Recording periods:	0 - 14 days, body weight: day 0, 7, 14

11 Statistics: not applicable

12.1 References: Noakes and Sanderson, 1969

13 Unpublished data: no unpublished data cited in this summary

EXAMPLE 2

Annex II A	Point addressed 5.3.2	Short term oral toxicity - 90 day

2	**Reference point:**	Volume 7, Section 3, Annex IIA, 5.3.2 / 01
3.1	**Authors:**	Report: X. Xxxxxxxxx, X. Xxxxxxxxxxx Addendum: X. Xxxxxx Summary: X. Xxxxxxxxxxxxx
3.2	**Title:**	XXX 1111 sub-chronic toxicity study on rats (three-month feeding experiment), and histopathological addendum
3.3	**Owner**	xxxxxxxxx
3.4	**Published:**	no
3.5	**Report No:**	xxxxxxx file No.: 0000 (report), 0000 (addendum)
3.6	**Date of report:**	June 4, 1980 (report), January 29, 1981 (addendum)
4.1	**Testing facility:**	Xxxxxxxxxxxx, Xxxxxxxxxxxxx, Xxxxxxxxxxxxxxxxxxxxxxx, Xxxxxxxxxx
4.2	**Lab. report No:**	xxxxx
5.1	**Dates of experimental work:**	November 1979 - February 1980
5.2	**Objectives:**	as title
6.1	**Test substance:**	XXX 1111, active substance as manufactured, 97.5 % pure, batch number: xxx
6.2	**Specification:**	as given in document J - specification number 4
6.3	**Storage stability:**	analysis performed at the beginning and at the end of the experimental phase, demonstrated that the active substance was stable.
6.4	**Stability in vehicle:**	analysis of diet conducted at the beginning of the study and twice during the experimental phase confirmed the stability of the active substance in the diet.
6.5	**Homogeneity in vehicle:**	Confirmed by concentration check: several sub-samples were measured and compared.
6.6	**Validity:**	not applicable

6.7 Physical form: pulverised chow

6.8 Vehicle / solvent: 50% premix in Wessalon S (= silica, CAS 7631-86-9) followed by dietary admixture to the food Altromin®

7.1 Test method: The method used was an in-house method. For details on the method used, see the description under 12 below.

7.2 Justification: When the study was performed, no particular method was compulsory. The method used complied to a great extent to then in force EPA Guidelines (Proposed Guidelines for Registering Pesticides in the US Federal Register, Vol. 43, No. 163, August 22, 1978). The method used differs from the prescribed method (Directive 87/302/EEC, Part B, sub-chronic oral toxicity test) in the following respects - brain weight was not recorded, skin and parathyroid were not investigated histologically. These deviations do not limit or impair the scientific validity of the study. The study design permits an accurate setting of a NOAEL and an elucidation of all relevant toxic effects.

7.3 Copy of method: Description of method used is included in the report. For details see also description below at point 12.

7.4 Choice of method: not applicable

7.5 Deviations: not applicable

8.1 Certified laboratory: not applicable

8.2 Certifying authority: not applicable

8.3 GLP: no

8.4 Justification: When the study was performed, GLP was not compulsory.

9.1 GEP: not applicable

9.2 Type of Facility (official or officially recognized): not applicable

9.3 Justification: not applicable

10 Test system -	**Animal species:**	Wistar rats (TNO W. 74)
	Source:	Winkelmann, Borchen, Germany
	Number of animals:	120 male, 120 female (30 per dosage group including two satellite groups of 5 animals each for testing possible enzyme induction at 7 and 28 days)
	Dosage (as):	0, 50, 100 and 500 ppm corresponding to: 3.24, 8.39 and 28.52 mg/kg bw/day in males, and 3.70, 9.83 and 32.97 mg/kg bw/day in females
	Administration:	oral by feeding
	Duration:	3 months
	General observations:	daily check for mortality and moribundity, daily cage-side observations for toxic signs (all animals)
	Food consumption:	measured weekly
	Body weight:	measured weekly
	Haematology:	erythrocyte count, leucocyte count, haemoglobin, MCV, MCH, MCHC, thrombocyte count, haematocrit, differential blood count, thromboplastin time (1, 3 months after initiation of treatment; 5 male and 5 female per group)
	Clinical chemistry:	alkaline phosphatase, aspartate aminotransferase, (blood) alanine aminotransferase, creatinine, urea, blood sugar, cholesterol, bilirubin, total protein (1, 3 months after initiation of treatment), glutamate dehydrogenase (only at termination of study; 5 male and 5 female per group)
	Enzyme induction assays:	N-demethylase activity, O-demethylase activity, cytochrome P 450 content (7 days, 28 days, 3 months; 5 male and 5 female per group)
	Urinalysis:	glucose, blood, protein, pH, ketone bodies, bilirubin, deposits (1, 3 months after initiating of the study; 5 male and 5 female per group)
	Gross pathology:	all animals which died during the study and all surviving rats; sacrifice via exsanguination in deep diethyl ether anaesthesia
	Organ weights:	thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, testes, ovaries (end of treatment; all animals)

Histopathology: heart, lungs, liver, spleen, kidneys, pancreas, pituitary, thyroid, adrenals, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, salivary glands, oesophagus, stomach, intestines (4 sections), lymph nodes, thymus, urinary bladder, brain, eyes, aorta, trachea, skeletal muscle, femur, bone marrow.

Histopathology was performed on 19 males and 20 females of the control group as well as on 20 males and 20 females of the highest dose group. The livers of 15 males and 15 females in the 30 ppm group and 15 males and 14 females in the mid group (100 ppm) were also examined.

11 Statistics: The values of the treated groups were compared with the control values by the Wilcoxon-Mann-Whitney U-test at the levels of significance $\alpha = 5\%$ and $\alpha = 1\%$.

12.1 References: no publications cited in this summary

13 Unpublished data: no unpublished data cited in this summary

EXAMPLE 3

Annex II A	Point Addressed 6.1	Metabolism, distribution and expression of residue in plants

2 Reference point: Volume 9, Section 4, Annex IIA, 6.1 / 03

3.1 Authors: Report: X.X. Xxxxxxx, X.X. Xxxxx Summary: X. xxxxxxxxxx

3.2 Title: Metabolism of XXX 1111 in potatoes

3.3 Owner: xxxxxxx

3.4 Published: no

3.5 Report No: xxxxxxxx File No.: 123456

3.6 Date of report: November 22, 1983, revised December 1, 1986

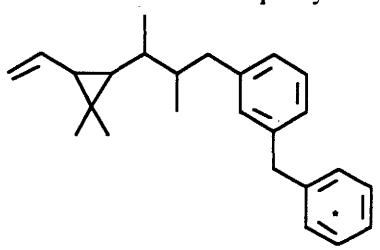
4.1 Testing facility: Xxxxxxxxx Xxxxxxxxxx Xxxxx, Xxxxxxxxx, Xxxxxx

4.2 Lab. report No: not applicable

5.1 Dates of experimental work: September, 1982 to April, 1983

5.2 Objectives: To determine the overall fate of XXX 1111 in mature potato plants; only the fluorophenoxy-benzyl portion of the compound was investigated since this portion is unique to XXX 1111

6.1 Test substance: ISO common name: XXX 1111, 99.8 % pure, batch number xxxx
Label: phenyl-UL-^{14}C



* indicates label position

6.2 Specification: Radiochemical purity: 99 %, 23.65 mCi/mmole

The compound used was a mixture of 4 diastereoisomeric enantiomers and had a *cis / trans* ratio of approximately 00/00, similar to that of the commercial material, which is approximately 00/00.

6.3	**Storage stability:**	not applicable
6.4	**Stability in vehicle:**	not applicable
6.5	**Homogeneity in vehicle:**	not applicable
6.6	**Validity:**	not applicable
6.7	**Physical form:**	emulsifiable concentrate
6.8	**Vehicle/solvent:**	200 EC xylene formulation carrier
7.1	**Test method:**	In house method. Guidelines were not available at the time the test was performed.
7.2	**Justification:**	The method was developed following discussions with regulatory officials from several European authorities and from EPA. The method used is consistent in all important respects to the methodology currently employed.
7.3	**Copy of method:**	description of methods included in report
7.4	**Choice of method:**	not applicable
7.5	**Deviations:**	not applicable
8.1	**Certified laboratory:**	not applicable
8.2	**Certifying authority:**	not applicable
8.3	**GLP:**	no
8.4	**Justification:**	when the study was performed, GLP was not required
9.1	**GEP:**	not applicable
9.2	**Type of Facility (official or officially recognized):**	not applicable
9.3	**Justification:**	not applicable

10 Test system -	**Test plants:**	seed potatoes (*Solanum tuberosum*)
	Test conditions:	greenhouse
	Time of treatment:	60 days after planting (initiation of blooming)
	Method of application:	spray (soil surface covered during treatment)
	Applied rate:	40 g as/40 l/ha (20.1 mg of [^{14}C] XXX 1111 in 0.1 ml of 200 EC xylene carrier dissolved in 19 ml of water)
	corresponding to:	approx. 100 g as/100 l/ha
	Sampling:	0, 42, 52, 80 and 98 days post treatment
	Analytical methods:	extraction with xxxx, filtered, liquid liquid extraction into xxxx, florisil column chromatography, followed by thin-layer chromatography and co-chromatography of standards, one-dimension on silica gel plates
	Radioactive areas on plates:	autoradiography
	Non-radioactive standards:	fluorescence quenching under short wavelength ultraviolet light.
	Radioassay:	Triton X-100 scintillation fluid, liquid scintillation spectrometer.

11 Statistics: not applicable

12.1 References: no publications cited in this summary

13 Unpublished data: no unpublished data cited in this summary

EXAMPLE 4

Annex II A	Point Addressed 7.1.3.2	Aged residue column leaching study

2 Reference point: Volume 18, Section 5, Annex IIA, 7.1.3.2 / 01

3.1 Authors: Report: X. Xxxxxxxx, X. Xxxxxxxxxxx
Summary: X. Xxxxxxx

3.2 Title: Leaching characteristics of substance aged in soil

3.3 Owner: xxxxxxxx

3.4 Published: no

3.5 Report No: Company file No.: 00000

3.6 Date of report: September 27, 1985

4.1 Testing facility: Xxxxxxxxxxxxxx, Xxxxxxxxxxxxxx, Xxxxxxxx, Xxxxxxxxxxxxxx

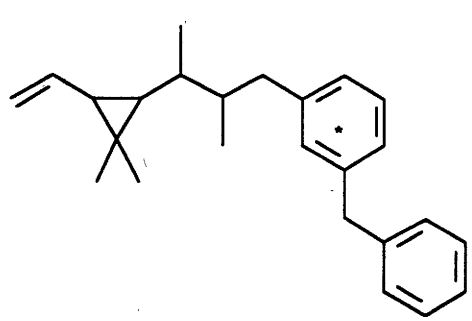
4.2 Lab. report No: not applicable

5.1 Dates of experimental work: August 1984 to January 1985

5.2 Objectives: as title

6.1 Test substance: ISO common name: XXX 1111,

a) radiolabelled: fluorobenzene-U-^{14}C, 99.8 % pure, batch number xxx.
Radiochemical purity: >00 %, 00 µCi/mg



* indicates label position

b) non-labelled: XXX 1111, as manufactured - used to increase the volume of the radiolabelled test material, 97.5 % pure, batch number xxxxxx

6.2 Specification:

a) radiolabelled: The compound used was a mixture of 4 diastereoisomeric enantiomers and had a *cis / trans* ratio of 00/00, similar to that of the commercial material, which is approximately 00/00.

b) non-labelled: as given in document J - specification No. 7

6.3 Storage stability: not applicable

6.4 Stability in vehicle: not applicable

6.5 Homogeneity in vehicle: not applicable (solution)

6.6 Validity: not applicable

6.7 Physical form: solution

6.8 Vehicle/solvent: acetone

7.1 Test method: Merkblatt (Bulletin) No. 37 of BBA - corresponds with the recommended SETAC method

7.2 Justification: not applicable

7.3 Copy of method: not relevant

7.4 Choice of method: not applicable

7.5 Deviations: none

8.1 Certified laboratory: no

8.2 Certifying authority: not applicable

8.3 GLP: no

8.4 Justification: When the study was performed, GLP was not required.

9.1 GEP: no

9.2 Type of Facility (official or officially recognized): not applicable

9.3 Justification: not applicable

10 Test system -

BBA standard soil 2.1:	(pH 7.0; 0.69 % org. C; 10.7 % fine particles < 20µ) 22 °C, 40 % maximum water holding capacity
Concentration:	0.5 mg as/ kg soil
Sampling:	0, 30 and 90 days
Thin-layer-chromatography and co-chromatography of standards:	one-dimension on silica gel plates
Radioactivity measurement:	liquid scintillation counting (fluids), linear analyzer (plates) or combustion (soil)

11 Statistics: none

12.1 References: no publications data cited in this summary

13 Unpublished data: no unpublished data cited in this summary

APPENDIX 5 - Part 1

FORM FOR USE IN REPORTING CROP RESIDUES DATA FROM INDIVIDUAL SUPERVISED TRIALS IN SUMMARY FORM

Active substance (common name) :
Crop/crop group :
Responsible body for reporting (name, address) :
Country :
Content of active substance (g/kg or g/L) :
Formulation (*e.g.* WP) :

Commercial Product (name) :
Producer of commercial product :
Indoor/Glasshouse/Outdoor :
Other active substance in the formulation (common name and content):
Residues calculated as :

1	2	3	4	5			6	7	8	9	10	11
Report No. Location (region)	Commodity/ Variety	Date of 1. Sowing or Planting 2. Flowering 3. Harvest	Method of treatment	Application rate per treatment			Dates of treatment(s) or no of treatment(s) and last date	Growth stage at last treatment or date	Portion analyzed	Residues (mg/kg)	PHI (days)	Remarks:
	(a)	(b)	(c)	kg as/hL	Water (L/ha)	kg as/ha	(d)	(e)	(a)		(f)	(g)

(a) According to EEC and Codex classifications (both) should be used
(b) Only if relevant
(c) High or low volume spaying, spreading, dusting *etc.*, overall, broadcast, type of equipment used must be indicated
(d) Year must be indicated
(e) BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4),
(f) Minimum number of days after last application (Label pre-harvest interval, PHI, underline)
(g) Remarks may include: Climatic conditions; Reference to analytical method; Information concerning the metabolites included, the method of storage, storage stability, analysis date

Note: All entries to be filled as appropriate

FIELD TRIALS, SOIL RESIDUE (SUMMARY)

Active substance :
Responsible body for reporting (name and address) :
Country :
Content of as Formulation :

Commercial Product (name) :
Producer of commercial product :
Residues calculated as :
Other as in formulation - common name and content) :

1	2	3	4	5	6	7	8	9	10	11	12
Report no Location (region)	Cropped or Bare	Soil Characteristics 1) soil texture 2) pH 3) % organic C 4) cation exchange capacity (meq/100 g)	Method of treatment (a)	Application rate per treatment (kg as/ha)	Application date (b)	Soil layer	Days after application	Residues (mg/kg) (c)	DT_{50} (days)	DT_{90} (days)	Remarks: (d)

(a) High or low volume spaying, spreading, dusting *etc.*, overall, broadcast, aerial spraying, row, individual plant, between plants - type of equipment used must be indicated
(b) Year must be indicated
(c) Results at or below the limit of determination should be identified *e.g.* < 0.01
(d) Remarks may include: climatic conditions, reference to analytical methods, information on the metabolites included, method of storage and storage stability, analysis date

Note: All entries to be filled as appropriate

APPENDIX 6

FORMAT FOR THE LISTING OF TEST AND STUDY REPORTS AND OTHER DOCUMENTATION

PART 1

LISTING BY ANNEX II AND ANNEX III POINT

1 As indicated in subparagraphs 3.1.1 (x) and (xii) and subparagraphs 3.2.1 (xi), (xii) and (xiii), the listing should cover each section of the dossier separately and should include:

- for each test and study report included in the complete dossier submitted, its title, source, company and report number;
- for each test and study report, an indication as to whether it is published or unpublished;
- for each test and study report, an indication as to whether it has been conducted in compliance with the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC, as appropriate;
- in the case of unpublished reports, an indication of the identity of the owner of the test or study concerned, where the owner is not the person or organization that submitted it; and
- in the case of unpublished reports an indication as to whether or not data protection is claimed in accordance with Article 13 of Directive 91/414/EEC, for the purposes of the authorization of preparations containing the active substance.

2 As specified in subparagraph 3.1.1 (xi) and subparagraph 3.2.1 (xii), in preparing the listing, applicants should conduct a detailed literature search - expert judgement is required to determine the nature and extent of the search to be conducted. The date on which the reference list was compiled, the identity of the data bases searched, the date range established for the purposes of the search (*e.g.* abstracts dated earlier than 1980 not requested), the language constraints, if any, imposed and the key words used for the purposes of the literature search, should be indicated.

3 For each Annex point or sub-point, the documents should be listed alphabetically by author and where for a particular author there is more than one report, they should be listed in chronological order - the most recent study being listed last. In cases where for a particular author, more than one reference is listed for any one year, the references should be distinguished by inserting letters after the year *i.e.* a, b, c, *etc.*, as appropriate.

4 Where data protection, in accordance with the provisions of Article 13 (3) (d) of the Directive is claimed, footnotes should be included to indicate that fact.

5 In the case of reports that are relevant to more than one point, sub-point or section, the entry should be repeated for each point for which it is relevant - the list that follows is intended to be illustrative of the required approach.

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 1 Listing by Annex Point of test and study reports and published papers submitted**

Reference List, by Annex Point **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Annex II Data and Information					
IIA, 5.1/01	Casida, J.E., Gaughan, L.C, Ruzo, L.O.	1979	Comparative metabolism of pyrethroids derived from 3-phenoxybenzyl and α-cyano-3-phenoxybenzyl alcohols. Advances in pesticide science, Fourth International Congress of Pesticide Chemistry, Zürich, Switzerland, July 24-38, 1978, part 2, 182-189 Not GLP, Published	N	-
IIA, 5.1/02	Chopade, H.M., McCann, S.A., Gentile, C.C.	1983	The distribution and metabolism of XXX 1111 in laying hens. Organics Inc Report No: MR86044 Not GLP, Unpublished	N	ORG
IIA, 5.1/03	Eben, A., Thyssen, J.	1981	Thiocyanate excretion in rats' urine after intraperitoneal administration of XXX 1111 and decamethrin in comparable doses and after exposure to defined XXX 1111 concentrations in the inhalation air. Organics Inc Report No: 10130 Not GLP, Unpublished	N	ORG
IIA, 5.1/04	Eben, A., Heimann, K.G, Machemer, L.	1982a	Comparative study of rats on absorption of XXX 1111 after single oral administration in polyethylene glycol 400 or cremophor El/water as formulation vehicle. Organics Inc Report No: 10715 Not GLP, Unpublished	N	ORG
IIA, 5.1/05	Eben, A., Machemer, L., Thyssen, J.	1982b	Comparative study of inhibition of the Na^+, K^+ and Mg^{++}-dependent ATPase from rats and chickens' brains in vitro by XXX 1722, some of its metabolites and further substances DDT, ouabain, some pyrethroids and phosphoric acid esters. Organics Inc Report No: 11116 Not GLP, Unpublished	N	ORG

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 1 Listing by Annex Point of test and study reports and published papers submitted**

Reference List, by Annex Point **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.1/06	Eben, A., Fuchs, R., Kurz, J., Wunsche, C., Flucke, W.	1987	Biotransformation of XXX 1111 in the chicken after oral administration of a high dose. Organics Inc Report No: 15849 GLP, Unpublished	N	ORG
IIA, 5.1/07	Ecker, W.	1982	Biotransformation of [Fluorbenzene ring- U-^{14}C]-XXX 1111; characterisation and provisional identification of metabolites. Organics Inc Report No: 10575 Not GLP, Unpublished	N	ORG
IIA, 5.1/08	Ecker, W.	1993	[Fluorobenzene-UL- ^{14}C]XXX 1111; [fluorobenzene-UL- ^{14}C]XXX 1111: metabolism part of the general metabolism study in the rat. Organics Inc Report No: 2059 GLP, Unpublished	N	ORG
IIA, 5.1/09	Klein, O., Weber, H., Suwelak, D.1	1983	[U-^{14}C]-C ([U-^{14}C]XXX 1111), fluorobenzene label): biokinetic part of the general metabolism study in the rat. Organics Inc Report No: 11872 Not GLP, Unpublished	N	ORG
IIA, 5.1/10	Miyamoto, L., Beynon, K.I., Roberts, T.R., Hemingway, R.J., Swaine, H.	1981	The chemistry, metabolism and residue analysis of synthetic pyrethroids. Pure & Appl. Chem., Vol. 53, pp. 1976-2022, 1981 Not GLP, Published	N	-
IIA, 5.1/11	Shaw, H.R., Ayers, J. E., McCann, S.A.	1983	Metabolism of XXX 1111 in a dairy cow. Organics Inc Report No: MR86043 Not GLP, Unpublished	N	ORG
IIA, 5.1/12	Weber, H., Suwelack, D.	1983	Fluorophenyl-U-^{14}C XXX 1111) biokinetic study on rats. Organics Inc Report No: PH11575(F) Not GLP, Unpublished	N	ORG

Reference List, by Annex Point | **Active Substance - XXX 1111** | **Company Name** | **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.2/01	Bomann, W.	1991	XXX 1111 / study for acute oral toxicity in rats. Organics Inc Report No: 19852 GLP, Unpublished	Y [10]	ORG
IIA, 5.2/02	Flucke, W., Thyssen, J.	1980a	XXX 1111 / acute toxicity studies. Organics Inc Report No: 8800 Not GLP, Unpublished	N	ORG
IIA, 5.2/03	Flucke, W., Thyssen, J.	1981	XXX 1111 (cis:trans isomer ratio = 11:11) / acute toxicity studies. Organics Inc Report No: 9673 Not GLP, Unpublished	N	ORG
IIA, 5.2/04	Heimann, K.G.	1982a	XXX 1111 / comparative tests for acute toxicity with various formulation aids. Organics Inc Report No: 10931 Not GLP, Unpublished	N	ORG
IIA, 5.2/05	Heimann, K.G	1982b	Determination of acute toxicity (LD_{50}). Organics Inc Not GLP, Unpublished	N	ORG
IIA, 5.2/06	Heimann, K.G.	1984	Determination of acute toxicity (LD_{50}). Organics Inc Not GLP, Unpublished	N	ORG
IIA, 5.2/07	Heimann, K.G.	1987	XXX 1111 / study for acute oral toxicity to rats (formulation acetone and peanut oil). Organics Inc Report No: 15847 GLP, Unpublished	N	ORG
IIA, 5.2/08	Hoffmann, K.	1981a	XXX 1111 / acute toxicity for sheep after oral administration. Organics Inc Report No: 9750 Not GLP, Unpublished	N	ORG

[10] protection for 5 years claimed from date of decision concerning listing in Annex I - the study report has not previously been submitted to any of the Member States in support of an application for authorization

Appendix 6 Format for the listing of test and study reports and other documentation — Part 1 Listing by Annex Point of test and study reports and published papers submitted

Reference List, by Annex Point | **Active Substance - XXX 1111** | **Company Name** | **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.2/09	Hoffmann, K.	1981b	XXX 1111 / Akute Toxizität am Hund nach oraler Verabreichung, Organics Inc Report No: Letter Not GLP, Unpublished	N	ORG
IIA, 5.2/10	Iyatomi, A., Watanabe, M., Ohta, K.	1982a	XXX 1111 / eye and skin irritation study on rabbits. Nihon Tokushu Noyaku Seizo Report No: 54165 Organics Inc Report No: 10365 Not GLP, Unpublished	N	NTN
IIA, 5.2/11	Iyatomi, A.	1982b	Report of acute toxicity - A. Nihon Tokushu Noyaku Seizo Report No: 5378 Organics Inc Report No: 10373 Not GLP, Unpublished	N	NTN
IIA, 5.2/12	Iyatomi, A.	1983	Report of acute toxicity - B. Nihon Tokushu Noyaku Seizo Report No: 59261 Organics Inc Report No: 11343 Not GLP, Unpublished	N	NTN
IIA, 5.2/13	Mihail, F.	1981a	XXX 1111 / intracutaneous sensitisation test on guinea pigs (Draize-test). Organics Inc Report No: 10222 Not GLP, Unpublished	N	ORG
IIA, 5.2/14	Mihail, F.	1981b	XXX 1111 / test for sensitising effect on guinea pigs (Maximization test according to Magnusson and Klingman). Organics Inc Report No: 10267 Not GLP, Unpublished	N	ORG
IIA, 5.2/15	Pauluhn, J., Thyssen, J.	1982	XXX 1111 / Study for acute inhalation toxicology (effect of formulation agent on inhalation). Organics Inc Report No: 10965 Not GLP, Unpublished	N	ORG
IIA, 5.2/16	Pauluhn, J., Kaliner, G.	1983	XXX 1111 / study for acute and subacute inhalation toxicity on chickens. Organics Inc Report No: 11558 Not GLP, Unpublished	N	ORG

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 1** **Listing by Annex Point of test and study reports and published papers submitted**

Reference List, by Annex Point **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.2/17	Pauluhn, J.	1987	XXX 1111 / study of the acute inhalation toxicity to rats using OECD guideline No. 403. Organics Inc Report No: 15612 GLP, Unpublished	N	ORG
IIA, 5.2/18	Pauluhn, J.	1988a	XXX 1111 / study for sensory irritant potential in the rat (RD_{50} determination). Organics Inc Report No: 16693 GLP, Unpublished	N	ORG
IIA, 5.2/19	Pauluhn, J.	1988b	XXX 1111 / study for sensory irritant potential in the mouse (RD_{50} determination). Organics Inc Report No: 16713 GLP, Unpublished	N	ORG
IIA, 5.2/20	Pauluhn, J.	1988c	XXX 1111 / study of the blood gases in rats. Organics Inc Report No: 16763 GLP, Unpublished	N	ORG
IIA, 5.2/21	Pauluhn, J.	1989	XXX 1111 / studies of acute inhalation toxicity in the mouse, in accordance with OECD guideline No. 403. Organics Inc Report No: 17765 GLP, Unpublished	Y [10]	ORG
IIA, 5.2/22	Sachsse, K.	1985a	Acute oral toxicity (LD_{50}) study with XXX 1111 (c.n. XXX 1111) vehicle: cremophor EL 2% in distilled water in the hen. Organics Inc Report No: R3621 GLP, Unpublished	N	ORG
IIA, 5.2/23	Sachsse, K.	1985b	Acute oral toxicity (LD_{50}) study with XXX 1111 vehicle: PEG 400 in the hen. Organics Inc Report No: R3622 GLP, Unpublished	N	ORG
IIA, 5.2/24	Thyssen, J., Kaliner, G., Gröning, P.	1981	XXX 1111 / neurotoxicity studies on hens. Organics Inc Report No: 9753 Not GLP, Unpublished	N	ORG

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 1** **Listing by Annex Point of test and study reports and published papers submitted**

Reference List, by Annex Point **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
IIA, 5.2/25	Thyssen, J.	1982	XXX 1111, formulation in water and influence on acute oral toxicity. Organics Inc Not GLP, Unpublished	N	ORG
IIA, 5.2/26	Watanabe, M., Iyatomi, A.	1984	Acute inhalation study of XXX 1111 on rats. Nihon Tokushu Noyaku Seizo Report No: 73126 Not GLP, Unpublished	N	NTN
IIA, 5.3/01	Flucke, W., Schilde, B.	1980b	XXX 1111 / subacute oral toxicity study on rats. Organics Inc Report No: 9039 Not GLP, Unpublished	N	ORG
IIA, 5.3/02	Löser, E., Schilde, B.	1980	XXX 1111 / subchronic toxicity study on rats (three-month feeding experiment). Organics Inc Report No: 9386 Not GLP, Unpublished	N	ORG

PART 2

LISTING BY AUTHOR

1 As in the case of the listing by Annex point of test and study reports and other documentation submitted (see Part 1 of Appendix 6), the listing should cover each section of the dossier separately and should include:

- for each test and study report included in the complete dossier submitted, its title, source, company and report number;
- for each test and study report, an indication as to whether it is published or unpublished;
- for each test and study report, an indication as to whether it has been conducted in compliance with the principles of GLP or the requirements of points 2.2 and 2.3 of the introduction to Annex II to Directive 93/71/EEC, as appropriate;
- in the case of unpublished reports, an indication of the identity of the owner of the test or study concerned, where the owner is not the person or organization that submitted it; and
- in the case of unpublished reports an indication as to whether or not data protection is claimed in accordance with Article 13 of Directive 91/414/EEC, for the purposes of the authorization of preparations containing the active substance.

2 As specified in subparagraph 3.1.1 (xi) and subparagraph 3.2.1 (xii), in preparing the listing, applicants should conduct a detailed literature search - expert judgement is required to determine the nature and extent of the search to be conducted. The date on which the reference list was compiled, the identity of the data bases searched, the date range established for the purposes of the search (*e.g.* abstracts dated earlier than 1980 not requested), the language constraints, if any, imposed and the key words used for the purposes of the literature search, should be indicated.

3 Within sections, the listing should be arranged alphabetically by author. Where for particular authors, there is more than one reference, they should be listed in chronological order. In cases where for a particular author, more than one reference is listed for any one year, the references should be distinguished by inserting letters after the year *i.e.* a, b, c, *etc.*, as appropriate.

4 Where data protection, in accordance with the provisions of Article 13 (3) (d) of the Directive is claimed, footnotes should be included to indicate that fact.

5 The reference lists that follow are intended to be illustrative of the required approach and relate to a fictitious compound, *active substance XXX 1111.*

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 2** **Listing by Author of test and study reports and published papers submitted**

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Annex II Data and Information					
Bomann, W.	IIA, 5.2/01	1991	XXX 1111 / study for acute oral toxicity in rats. Organics Inc Report No: 19852 GLP, Unpublished	Y [11]	ORG
Casida, J.E., Gaughan, L.C, Ruzo, L.O.	IIA, 5.1/01	1979	Comparative metabolism of pyrethroids derived from 3-phenoxybenzyl and α-cyano-3-phenoxybenzyl alcohols. Advances in pesticide science, Fourth International Congress of Pesticide Chemistry, Zürich, Switzerland, July 24-38, 1978, part 2, 182-189 Not GLP, Published	N	-
Chopade, H.M., McCann, S.A., Gentile, C.C.	IIA, 5.1/02	1983	The distribution and metabolism of XXX 1111 in laying hens. Organics Inc Report No: MR86044 Not GLP, Unpublished	N	ORG
Eben, A., Fuchs, R., Kurz, J., Wunsche, C., Flucke, W.	IIA, 5.1/06	1987	Biotransformation of XXX 1111 in the chicken after oral administration of a high dose. Organics Inc Report No: 15849 GLP, Unpublished	N	ORG
Eben, A., Heimann, K.G, Machemer, L.	IIA, 5.1/04	1982a	Comparative study of rats on absorption of XXX 1111 after single oral administration in polyethylene glycol 400 or cremophor El/water as formulation vehicle. Organics Inc Report No: 10715 Not GLP, Unpublished	N	ORG

[11] protection for 5 years claimed from date of decision concerning listing in Annex I - the study report has not previously been submitted to any of the Member States in support of an application for authorization

Appendix 6 Format for the listing of test and study reports and other documentation — **Part 2** Listing by Author of test and study reports and published papers submitted

Reference List, by Author | **Active Substance - XXX 1111** | **Company Name** | **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Eben, A., Machemer, L., Thyssen, J.	IIA, 5.1/05	1982b	Comparative study of inhibition of the Na^+, K^+ and Mg^{++}-dependent ATPase from rats and chickens' brains in vitro by XXX 1722, some of its metabolites and further substances DDT, ouabain, some pyrethroids and phosphoric acid esters. Organics Inc Report No: 11116 Not GLP, Unpublished	N	ORG
Eben, A., Thyssen, J.	IIA, 5.1./03	1981	Thiocyanate excretion in rats' urine after intraperitoneal administration of XXX 1111 and decamethrin in comparable doses and after exposure to defined XXX 1111 concentrations in the inhalation air. Organics Inc Report No: 10130 Not GLP, Unpublished	N	ORG
Ecker, W.	IIA, 5.1/07	1982	Biotransformation of [Fluorbenzene ring- U-^{14}C]-XXX 1111; characterisation and provisional identification of metabolites. Organics Inc Report No: 10575 Not GLP, Unpublished	N	ORG
Ecker, W.	IIA, 5.1/08	1993	[Fluorobenzene-UL-^{14}C]XXX 1111; [fluorobenzene-UL-^{14}C]XXX 1111: metabolism part of the general metabolism study in the rat. Organics Inc Report No: 2059 GLP, Unpublished	N	ORG
Flucke, W., Schilde, B.	IIA, 5.3/01	1980b	XXX 1111 / subacute oral toxicity study on rats. Organics Inc Report No: 9039 Not GLP, Unpublished	N	ORG
Flucke, W., Thyssen, J.	IIA, 5.2/02	1980a	XXX 1111 / acute toxicity studies. Organics Inc Report No: 8800 Not GLP, Unpublished	N	ORG
Flucke, W., Thyssen, J.	IIA, 5.2/03	1981	XXX 1111 (cis:trans isomer ratio = 11:11) / acute toxicity studies. Organics Inc Report No: 9673 Not GLP, Unpublished	N	ORG

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 2** **Listing by Author of test and study reports and published papers submitted**

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Heimann, K.G	IIA, 5.2/05	1982b	Determination of acute toxicity (LD_{50}). Organics Inc Not GLP, Unpublished	N	ORG
Heimann, K.G	IIA, 5.2/04	1982a	XXX 1111 / comparative tests for acute toxicity with various formulation aids. Organics Inc Report No: 10931 Not GLP, Unpublished	N	ORG
Heimann, K.G	IIA, 5.2/06	1984	Determination of acute toxicity (LD_{50}). Organics Inc Not GLP, Unpublished	N	ORG
Heimann, K.G	IIA, 5.2/07	1987	XXX 1111 / study for acute oral toxicity to rats (formulation acetone and peanut oil). Organics Inc Report No: 15847 GLP, Unpublished	N	ORG
Hoffmann, K.	IIA, 5.2/08	1981a	XXX 1111 / acute toxicity for sheep after oral administration. Organics Inc Report No: 9750 Not GLP, Unpublished	N	ORG
Hoffmann, K.	IIA, 5.2/09	1981b	XXX 1111 / Akute Toxizität am Hund nach oraler Verabreichung. Organics Inc Report No: Letter Not GLP, Unpublished	N	ORG
Iyatomi, A.	IIA, 5.2/11	1982b	Report of acute toxicity - A. Nihon Tokushu Noyaku Seizo Report No: 5378 Organics Inc Report No: 10373 Not GLP, Unpublished	N	NTN
Iyatomi, A.	IIA, 5.2/12	1983	Report of acute toxicity - B. Nihon Tokushu Noyaku Seizo Report No: 59261 Organics Inc Report No: 11343 Not GLP, Unpublished	N	NTN

Appendix 6 Format for the listing of test and study reports and other documentation — **Part 2** Listing by Author of test and study reports and published papers submitted

Reference List, by Author | **Active Substance - XXX 1111** | **Company Name** | **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Iyatomi, A., Watanabe, M., Ohta, K.	IIA, 5.2/10	1982a	XXX 1111 / eye and skin irritation study on rabbits. Nihon Tokushu Noyaku Seizo Report No: 54165 Organics Inc Report No: 10365 Not GLP, Unpublished	N	NTN
Klein, O., Weber, H., Suwelak, D.1	IIA, 5.1/09	1983	[U-^{14}C]-C ([U-^{14}C]XXX 1111), fluorobenzene label): biokinetic part of the general metabolism study in the rat. Organics Inc Report No: 11872 Not GLP, Unpublished	N	ORG
Löser, E., Schilde, B.	IIA, 5.3/02	1980	XXX 1111 / subchronic toxicity study on rats (three-month feeding experiment). Organics Inc Report No: 9386 Not GLP, Unpublished	N	ORG
Mihail, F.	IIA, 5.2/13	1981a	XXX 1111 / intracutaneous sensitisation test on guinea pigs (Draize-test). Organics Inc Report No: 10222 Not GLP, Unpublished	N	ORG
Mihail, F.	IIA, 5.2/14	1981b	XXX 1111 / test for sensitising effect on guinea pigs (Maximization test according to Magnusson and Klingman). Organics Inc Report No: 10267 Not GLP, Unpublished	N	ORG
Miyamoto, L., Beynon, K.I., Roberts, T.R., Hemingway, R.J., Swaine, H.	IIA, 5.1/10	1981	The chemistry, metabolism and residue analysis of synthetic pyrethroids. Pure & Appl. Chem., Vol. 53, pp. 1976-2022, 1981 Not GLP, Published	N	-
Pauluhn, J.	IIA, 5.2/17	1987	XXX 1111 / study of the acute inhalation toxicity to rats using OECD guideline No. 403. Organics Inc Report No: 15612 GLP, Unpublished	N	ORG

Appendix 6 **Format for the listing of test and study reports and other documentation** **Part 2** **Listing by Author of test and study reports and published papers submitted**

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Pauluhn, J.	IIA, 5.2/18	1988a	XXX 1111 / study for sensory irritant potential in the rat (RD_{50} determination). Organics Inc Report No: 16693 GLP, Unpublished	N	ORG
Pauluhn, J.	IIA, 5.2/19	1988b	XXX 1111 / study for sensory irritant potential in the mouse (RD_{50} determination). Organics Inc Report No: 16713 GLP, Unpublished	N	ORG
Pauluhn, J.	IIA, 5.2/20	1988c	XXX 1111 / study of the blood gases in rats. Organics Inc Report No: 16763 GLP, Unpublished	N	ORG
Pauluhn, J.	IIA, 5.2/21	1989	XXX 1111 / studies of acute inhalation toxicity in the mouse, in accordance with OECD guideline No. 403. Organics Inc Report No: 17765 GLP, Unpublished	Y [11]	ORG
Pauluhn, J., Kaliner, G.	IIA, 5.2/16	1983	XXX 1111 / study for acute and subacute inhalation toxicity on chickens. Organics Inc Report No: 11558 Not GLP, Unpublished	N	ORG
Pauluhn, J., Thyssen, J.	IIA, 5.2/15	1982	XXX 1111 / Study for acute inhalation toxicology (effect of formulation agent on inhalation). Organics Inc Report No: 10965 Not GLP, Unpublished	N	ORG
Sachsse, K.	IIA, 5.2/22	1985a	Acute oral toxicity (LD_{50}) study with XXX 1111 (c.n. XXX 1111) vehicle: cremophor EL 2% in distilled water in the hen. Organics Inc Report No: R3621 GLP, Unpublished	N	ORG
Sachsse, K.	IIA, 5.2/23	1985b	Acute oral toxicity (LD_{50}) study with XXX 1111 vehicle: PEG 400 in the hen. Organics Inc Report No: R3622 GLP, Unpublished	N	ORG

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point / reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N	Owner
Shaw, H.R., Ayers, J. E., McCann, S.A.	IIA, 5.1/11	1983	Metabolism of XXX 1111 in a dairy cow. Organics Inc Report No: MR86043 Not GLP, Unpublished	N	ORG
Thyssen, J.	IIA, 5.2/25	1982	XXX 1111, formulation in water and influence on acute oral toxicity. Organics Inc Not GLP, Unpublished	N	ORG
Thyssen, J., Kaliner, G., Gröning, P	IIA, 5.2/24	1981	XXX 1111 / neurotoxicity studies on hens. Organics Inc Report No: 9753 Not GLP, Unpublished	N	ORG
Watanabe, M., Iyatomi, A.	IIA, 5.2/26	1984	Acute inhalation study of XXX 1111 on rats. Nihon Tokushu Noyaku Seizo Report No: 73126 Not GLP, Unpublished	N	NTN
Weber, H., Suwelack, D.	IIA, 5.1/18	1983	Fluorophenyl-U-^{14}C XXX 1111) biokinetic study on rats. Organics Inc Report No: PH11575(F) Not GLP, Unpublished	N	ORG

PART 3

LISTING OF TEST AND STUDY REPORTS AND PUBLISHED PAPERS NOT SUBMITTED

1 As in the case of the listing of test and study reports and other documentation submitted (see Parts 1 and 2 of Appendix 6), the listing of test and study reports and published papers not submitted as part of the complete dossier, should cover each section of the dossier separately and should include:

- for each test and study report, its title, source, company and report number;
- for each test and study report, an indication as to whether it is published or unpublished; and
- for each test and study report, an indication as to the reason the test or study report or published paper was not submitted;

2 Within sections, the listing should be arranged alphabetically by author. Where for particular authors, there is more than one reference, they should be listed in chronological order. In cases where for a particular author, more than one reference is listed for any one year, the references should be distinguished by inserting letters after the year *i.e.* a, b, c, *etc.*, as appropriate.

3 The reference lists that follow are intended to be illustrative of the required approach and relate to a fictitious compound, *active substance XXX 1111.*

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point	Year	Title Source (where different from company) Company, Report No Indication of the reason not submitted Published or not	Data Protection Claimed Y/N	Owner
Becker, H.	IIA, 5.6.2	1983	Dose-finding embryotoxicity (including teratogenicity) study with XXX 1111 in the rat (preliminary study) Organics Inc Report No. R8128 Provides no useful information. Unpublished	N	ORG
Becker, H.	IIA, 5.6.2	1992a	Second dose range-finding embryotoxicity study (including teratogenicity) with XXX 1111 in the rabbit Organics Inc Report No. R5513 Provides no useful information. Unpublished	N	ORG
Becker, H.	IIA, 5.6.2	1993	Dose-finding embryotoxicity (including teratogenicity) study with XXX 1111 in the rat (preliminary study) Organics Inc Report No. R5980 Provides no useful information. Unpublished	N	ORG
Becker, H., Biedermann, K.	IIA, 5.6.2	1992b	Dose range-finding embryotoxicity study (including teratogenicity) with XXX 1111 in the rabbit Organics Inc Report No. R5512 Provides no useful information. Unpublished	N	ORG
Flucke, W.	IIA, 5.2.1	1980	XXX 1111, diastereomers - determination of the acute toxicity (LD_{50}) Organics Inc Report No. R1398 Method used no longer accepted. Unpublished	N	ORG
Heimann, K.G.	IIA, 5.2.6	1982	Comparative study of Ethyl-4-Aminobenzoate, Formaldehyde, Potassium Penicillin G, and XXX 1111 to test for sensitisation effect using various test methods (Sensitization tests of Draize, Magnusson and Klingman, and Maurer) Organics Inc Report No. 10812 Method used no longer accepted. Unpublished	N	ORG
Heimann, K.G.	IIA, 5.2.2	1984	XXX 1111 - determination of acute toxicity (LD50) (Lutrol) Organics Inc Report No R2542, September 25, 1984 Method used no longer accepted. Unpublished	N	ORG

Reference List, by Author **Active Substance - XXX 1111** **Company Name** **Month & Year List Compiled**

Section 3, Toxicological and Metabolism Studies on the Active Substance (Annex IIA, Point 5)

Author(s)	Annex point	Year	Title Source (where different from company) Company, Report No Indication of the reason not submitted Published or not	Data Protection Claimed Y/N	Owner
Kazda, S.	IIA. 5.8.2	1979	XXX 1111 - Effect on arterial blood pressure and heart rate Organics Inc Report No. R7359 Test material not identified. Unpublished	N	ORG
Marshall, J.A.	IIA, 5.8.2	1985	Effects of pyrethroids on reactions of rats. Fund. Appl. Toxicol. 8, 742 - 748 Study design statistically faulty. Published	N	-
Mihail, F.L.	IIA, 5.2.1	1978	XXX 1111 - TOX I Organics Inc Report No. R8472 Test material not identified. Unpublished	N	ORG
Roberts. M.J.	IIA, 5.7	1981	Impact of pyrethroid insecticides on vertebrates. Neuropathol. Appl. Neurobiol. 6, 285 - 289 Test material not identified. Published	N	-
Sanders, W.H.	IIA, 5.7	1986	Toxicological properties of pyrethroids. Critical Reviews in Toxicology 18, 286 - 291, Test material not identified. Published	N	-

APPENDIX 7

FORMAT FOR THE COMPILATION OF *TIER II* SUMMARIES - ANNEX II

PART 1

Section 1 **Identity of the Active Substance; Physical and Chemical Properties of the Active Substance; Further Information on the Active Substance; Proposals including Justification of the Proposals for the Classification and Labelling of the Active Substance (Annex II, points 1 to 3 and 10)**

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

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2 Physical and chemical properties of the active substance

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Melting point, freezing point or solidification point (IIA 2.1.1)	OECD 102	XXXX, 98.5% pure, specification 4, Document J	melting point = 117 - 119 °C	OECD 102 is equivalent to EEC A.1	Y	Johnson, 1995
Boiling point (IIA 2.1.2)						
Temperature of decomposition of sublimation (IIA 2.1.3)						
Relative density (IIA 2.2)						
Vapour pressure (IIA 2.3.1)						
Henry's law constant (IIA 2.3.2)						

Appendix 7 **Format for the Compilation of *Tier II* Summaries - Annex II** **Part 1 Section 1**

Company name **Month and year** **Active Substance (Name)** **page of**

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Colour and physical state (IIA 2.4.1)						
Odour (IIA 2.4.2)						
UV/VIS, IR, NMR, MS spectra (as) (IIA 2.5.1)						
UV/VIS, IR, NMR, MS spectra (impurities) (IIA 2.5.2)						
Solubility in water (IIA 2.6)						
Solubility in organic solvents (IIA 2.7)						
n-octanol/water partition co-efficient (IIA 2.8)						
Hydrolysis rate at pH 4,7 and 9 under sterile conditions in the absence of light (IIA 2.9.1)						
Direct photo-transformation (IIA 2.9.2)						
Quantum yield of direct photo-transformation (IIA 2.9.3)						
Dissociation constant (IIA 2.9.4)						
Estimated photochemical oxidative degradation (IIA 2.10)						
Flammability (IIA 2.11.1)						

Company name Month and year Active Substance (Name) page of

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Auto-flammability (IIA 2.11.2)						
Flash point (IIA 2.12)						
Explosive properties (IIA 2.13)						
Surface Tension (IIA 2.14)						
Oxidizing properties (IIA 2.15)						

Summary and Conclusions

XXXX is a herbicide with xxxxxxxxxxx structure consisting of two diastereoisomers. Its vapour pressure and volatility are low. Due to its basic properties the water solubility of XXXX varies in the range between pH 3 and 9 from very soluble to soluble. At < 3 its log P_{ow} is not critical in respect to ecological impact and environmental behaviour. Hydrolysis and photolysis are only of minor importance in its degradation in the environment. Its flammability, explosive and oxidizing properties are not critical.

PART 2

Section 2 Analytical methods (Annex II, Point 4.1 and 4.2)

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

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4.2 Methods for the determination of residues

Matrix	Method	Limit of quantification	Reference
crops	GC-ECD		Peter and Paul, 1992
wheat		0.01 mg/kg	
grape		0.05 mg/kg	
crops	GC-ECD		Hinz and Kunz, 1993
wheat		0.01 mg/kg	
grape		0.05 mg/kg	
milk	GC-PND	0.01 mg/kg	Paul and Mary, 1992
meat, egg	GC-PND	0.05 mg/kg	Paul and Mary, 1992
soil	HPLC-UV	0.05 mg/kg	Mary and Peter, 1992
water	GC-MS	0.05 µg/l	Herbert, 1993
air	HPLC-UV	0.3 µg/m³	Louise et al., 1994
blood	GC-MS	0.1 µg/l	Laura and Sean, 1995

4.2.1 Residues in and/or on plants, plant products, foodstuffs (of plant and animal origin), feedingstuffs

4.2.1.1 Description of methods

Peter and Paul, 1992

Residues of xxx in plant material (wheat, grape) were determined according to standard-multi-method DFG S 19 (Specht and Thier, 1987) and supplements to the method (Peter and Paul, 1992). xxx was extracted from the sample material with acetone/water. Water was added in an amount such that, taking into account the water content of the sample, the acetone/water ratio was 2/1. Sodium chloride and dichloromethane were added to the extract leading to a separation of the organic and the aqueous phase. In accordance with the on-line version, cyclohexane/ethyl acetate can be substituted for dichloromethane. The organic phase was evaporated and a cleanup of the residue achieved using gel chromatography with Bio-Beads S-X3. Elution was done with a cyclohexane/ethyl acetate mixture. The fraction containing the residues of xxx was further cleaned on a silica gel column eluted with toluene/acetone. The active substance was determined by gas chromatography with an electron capture detector.

Hinz and Kunz, 1993

The method of Peter and Paul (1992) was validated by Hinz and Kunz (1993). During the inter laboratory validation exercise, two minor modifications to the original method were introduced. In addition, the detector linearity study curve was determined at a standard concentration of 0.025 mg/kg. The second modification was in the ratio of acetone/water used - it was increased from 2:1 to 2.5:1.

Paul and Mary, 1992

Residues of xxx in animal tissues, eggs and milk were determined by gas-chromatography. xxx was extracted from tissue samples and eggs with acetonitrile. An aliquot of the extract was cleaned up using gel permeation chromatography (GPC) followed by elution through alumina and Florisil solid phase extraction cartridges. The eluate was evaporated to dryness and taken up in a known volume of acetone for analysis by gas-chromatography with phosphorus-nitrogen-detection (GC-PND). xxx residues in milk samples were extracted using acetonitrile and partitioned into dichloromethane. The extract was cleaned as described for animal tissue and eggs.

4.2.1.2 Validation data for analytical methods for the determination of residues of xxx in food of plant and animal origin

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Peter and Paul, 1992	wheat	0.01*	95	85-109	8.2	8
		0.1	87	80-97	6.1	8
	grape	0.05*	102	99-110	4.2	10
		0.1	99	98-100	1.0	6
Hinz and Kunz, 1993	wheat	0.01*	90	85-100	7.2	4
		0.1	89	83-99	9.3	4
	grape	0.05*	102	100-107	3.5	4
		0.1	92	88-94	3.0	4
Paul and Mary, 1992	milk	0.01*	88	85-100	9.8	6
		0.2	93	86-107	14.2	6
	eggs	0.05*	86	78-93	12.3	6
		1.0	91	90-93	2.0	3
	muscle	0.05*	78	75-80	3.4	6
		1.0	84	80-90	5.0	3
	liver	0.05*	80	73-86	7.3	3

* Limit of quantification, defined by the lowest validated fortification level.

4.2.2 Residues in soil

4.2.2.1 Description of method

Mary and Peter, 1992

xxx and its major soil metabolite (xyz123) can be determined using high performance liquid chromatography (HPLC). The analytes in soil samples were extracted with methanol/water. An aliquot of the extract was then subjected to liquid-liquid partitioning using an acidified sodium chloride solution and dichloromethane. The dichloromethane extract was evaporated to dryness and taken up in a known volume of HPLC mobile phase (acetonitrile/water, gradient) and was analysed by high performance liquid chromatography using UV detection. Quantitative confirmation of residues present may be carried out using HPLC with triple quadrupole mass spectrometry. The method can be run either manually or automated as a robotic system.

4.2.2.2 Validation data for analytical methods for the determination of residues of xxx in soil

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Mary and Peter 1992						
(xxx)	soil	0.05	102	99-110	4.2	10
		0.1	99	98-100	1.0	6
		0.5	88	85-100	9.8	6
(xyz123)	soil	0.05	86	78-93	12.3	6
		0.1	91	90-93	2.0	3
		0.5	80	73-86	7.3	3

PART 3

Section 3 Toxicological and Metabolism Studies on the Active Substance (Annex II, Point 5)

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

5.2 Acute toxicity

5.2.1 Oral

Report: Glaza, S.M. (1993c); Acute oral toxicity of technical XXX-YYYYYY in rats; Hazleton Wisconsin, Madison, WI, USA; unpublished report no. HWI21201693, 19.04.1993; dates of experimental work: 04.01.1993 to 19.04.1993.

Guidelines: EPA FIFRA, subdivision F, §81-1 (equivalent to EEC method B.2 - Directive 92/69/EEC); deviations: none except that the limit dose was 5000 mg/kg instead of 2000 mg/kg

GLP: Yes (self certification by the laboratory) [12]

Material and methods: Test material: XXX-YYYYYY; Batch FL-921658; Purity: 95.0 % [13]. The test material was suspended in distilled water and administered to groups of 5 male and 5 female fasted Crl:CD®BR rats by oral gavage at a dose level of 5000 mg/kg (application volume 10 ml/kg).

Findings: No mortalities were observed (Table 5.2.1-1) Except for one male which had a soft stool at one hour after dosing, no clinical signs were observed throughout the observation period. No effects on body weight development were noted. At gross necropsy no visible lesions were observed.

[12] In the US, laboratories are responsible for certifying that they have complied with FIFRA GLP requirements. Compliance is verified by the EPA (Environmental Protection Agency, Office of Compliance Monitoring) by means of periodic inspections.

[13] Details with respect to the purity and content of impurities of the test material are provided in Document J

Table 5.2.1-1: Acute oral toxicity of XXX-YYYYYY

Males			Females		
Dose	Mortality	Time of death	Dose	Mortality	Time of death
5000 mg/kg	0/5	-	5000 mg/kg	0/5	-

Conclusion: The oral LD_{50} of the test compound in rats was determined to be greater than 5000 mg/kg. In according with the provisions of Council Directive 67/548/EEC, classification is not required.

5.2.2 Percutaneous

Report: Glaza, S.M. (1993d), Acute dermal toxicity of technical XXX-YYYYYY in rabbits, Hazleton Wisconsin, Madison, WI, USA, unpublished report No. HWI21201694, 19.04.1993; dates of experimental work: 12.01.1993 to 19.04.1993.

Guidelines: EPA FIFRA, Subdivision F, §81-2 (equivalent to EEC method B.3 - Directive 92/69/EEC); deviations: none

GLP: Yes (self certification by the laboratory) [12]

Material and methods: Test material: XXX-YYYYYY; Batch FL-921658; Purity: 95.0 % [13]. The moistened (0.9% saline) test material was applied to the shaved skin of Hra:(NZW) SPF rabbits at a dose level of 2000 mg/kg and held in place with an occlusive wrapping.

Findings: No mortalities or clinical symptoms of systemic toxicity were observed during the study period. Body weights were unaffected by treatment. No visible lesions were observed at gross necropsy. One female rabbit was inadvertently sacrificed and necropsied on day 7 instead of day 14.

Table 5.2.2-1: Acute dermal toxicity of XXX-YYYYYY

Males			Females		
Dose	Mortality	Time of death	Dose	Mortality	Time of death
2000 mg/kg	0/5	-	2000 mg/kg	0/5	-

Conclusion: The dermal LD_{50} of the test compound in rabbits was determined to be greater than 2000 mg/kg. In according with the provisions of Council Directive 67/548/EEC, classification is not required.

5.2.3 Inhalation

Report: Hartmann, H.R. (1993), XXX-YYYYYY - acute inhalation toxicity in the rat, Short-term Toxicology, Ciba-Geigy Ltd., 4332 Stein, Switzerland; unpublished report No. 921200, 11.11.1993; dates of experimental work: 08.09.1993 to 22.09.1993

Guidelines: OECD 403, EEC method B.2 - Directive 92/69/EEC; deviations: none

GLP: Yes (certified laboratory)

Material and methods: Test material: XXX-YYYYYY; Batch P.208009; Purity 95.6 % [13]; Groups of 5 male and 5 female Tif:RAIf (SPF) rats were exposed to the test material. The main exposure parameters were as follows -

Parameter	Value
Flow rate (whole system)	48 L/min
Flow rate (individual tube)	2 L/min
Nominal concentration	5241 mg/m^3
Analytical concentration	5082 ± 141 mg/m^3 (n=5)
Particle size MAAD/GSD	3.4 µm/2.2
Particles < 7 µm (% w/w)	82
Particles < 3 µm (% w/w)	44

Findings: No mortalities were recorded during the study (Table 5.2.3-1). Clinical signs in both sexes included piloerection, hunched posture, and dyspnea, which cleared by day 3. Body weight gain was in the expected range and comparable to that of control rats. There were no observable abnormalities at gross necropsy.

Table 5.2.3-1: Acute inhalation toxicity of XXX-YYYYYY

Males			Females		
Dose	Mortality	Time of death	Dose	Mortality	Time of death
5082 mg/kg	0/5	-	5082 mg/kg	0/5	-

Conclusion: The acute inhalation LC_{50} of the test material in albino rats was determined to be greater than 5082 mg/m^3. In according with the provisions of Council Directive 67/548/EEC, classification is not required.

5.2.4 Skin irritation

Report: Glaza, S.M. (1993a); Primary dermal irritation of CGA-277476 technical in rabbits; Hazleton Wisconsin, Madison, WI, USA; unpublished report No. HWI21201695, 11.03.1993; dates of experimental work: 11.01.1993 to 14.01.1993.

Guidelines: EPA FIFRA, Subdivision F §81-5 (equivalent to EEC method B.4 - Directive 92/69/EEC);); deviations: 6 instead of 3 rabbits were used - a regulatory requirement in the USA.

GLP: Yes (self certification by the laboratory) [12]

Materials and methods: Test material: XXX-YYYYYY; Batch FL-921658; Purity: 95.0 % [13]; The moistened test material (0.9% saline) was applied to the shaved skin of 4 male and 2 female Hra: (NZW) SPF rabbits. The application area was covered with a 2.5 x 2.5 cm gauze pad secured with paper tape and overwrapped to provide a semiocclusive dressing.

Findings: Very slight (barely perceptible) erythema was observed in 2/6 rabbits, 4 hours after application. No signs of skin irritation were present at 24, 48 and 72 hours (Table 5.2.4-1).

Table 5.2.4-1: Individual and mean skin irritation scores according to the Draize scheme

	Erythema						Oedema					
Animal no	44529	44530	44531	44478	44448	44286	44529	44530	44531	44478	44448	44286
after 4 hr	0	1	0	1	0	0	0	0	0	0	0	0
after 24 hr	0	0	0	0	0	0	0	0	0	0	0	0
after 48 hr	0	0	0	0	0	0	0	0	0	0	0	0
after 72 hr	0	0	0	0	0	0	0	0	0	0	0	0
mean score 24-72 h	0.0						0.0					
Additional criteria specified in Directive 93/21/EEC Point 3.2.6.1 fulfilled: Yes/No												

Conclusion: On the basis of the degree of skin reaction observed (mean skin irritation scores 24 to 72 hours after removal of the test article), and the criteria specified in Council Directive 67/548/EEC, the test compound does not classify as a skin irritant

5.2.5. Eye irritation

Report: Glaza, S.M. (1993b); Primary eye irritation of technical XXX-YYYYYY in rabbits; Hazleton Wisconsin, Madison, WI, USA; unpublished report No. HWI21201696, 11.03.1993; dates of experimental work: 11.01.1993 to 16.01.1993

Guidelines: EPA FIFRA, Subdivision F §81-4 (equivalent to EEC method B.5 - Directive 92/69/EEC); deviations: 9 instead of 3 rabbits were used, the eyes of six rabbits remained unwashed (regulatory requirement in the USA); the eyes of the remaining 3 animals were washed 30 seconds after instillation of the test article.

GLP: Yes (self certification by the laboratory) [12]

Materials and methods: Test material: XXX-YYYYYY; Batch FL-921658; Purity: 95.0 % [13]. Each Hra:(NZW) SPF rabbit received 0.03 g (weight equivalent of 100 µl) of XXX-YYYYYY, placed into the elevated lower lid of the right eye.

Findings: Slight conjunctival redness was observed in the unwashed eyes of 2/6 rabbits 1 hour after application. No signs of irritation were present at 24, 48 and 72 hours in unwashed eyes (Table 5.2.5-1). In washed eyes no signs of ocular irritation were noted 1, 24, 48 and 72 hours after instillation.

Table 5.2.5-1: Eye irritation scores according to the Draize scheme - unwashed eyes

	Cornea						Iris						Conjunctiva-redness						Conjunctiva-chemosis					
Time/ Rabbit	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1 hour	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
24 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
mean scores 24-72 h	0.0						0.0						0.0						0.0					
Additional criteria in Directive 93/21/EEC Point 3.2.6.2 fulfilled: Yes/No																								

Conclusion: On the basis of reactions observed (mean eye irritation scores 24 to 72 hours after instillation of the test article), and the criteria specified in Council Directive 67/548/EEC, the test compound does not classify as an eye irritant.

5.2.6 Skin sensitization

Two sensitization studies were carried out: a non-adjuvant 'Closed Patch test' (according to Buehler) and an adjuvant 'Maximization test' according to Magnusson and Klingman.

5.2.6.1 Closed Patch test

Report: Glaza, S.M. (1993e); Dermal sensitization study of XXX-YYYYYY technical in Guinea pigs - Closed Patch technique; Hazleton Wisconsin, Madison, WI, USA; unpublished report No. HWI21204587, 30.04.1993; dates of experimental work: 12.01.1993 to 15.02.1993.

Guidelines: EPA FIFRA, Subdivision F, §81-6 (equivalent to EEC method B.6 - Buehler test - Directive 92/69/EEC); deviations: the test group consisted of only 10 animals. The positive control group consisted of only 4 animals. A group of 10 naive (previously untreated) control animals were used as a negative control group. It is not considered that these deviations effect the validity of the study.

GLP: Yes (self certification by the laboratory) [12]

Material and methods: Test material: XXX-YYYYYY; Batch FL-921658; Purity: 95.0 % [13]. In a preliminary irritation screen, no signs of dermal irritation with 25, 50, 75% or undiluted material were revealed. Accordingly the undiluted test article (*i.e.* the maximum subirritant concentration) was used for induction and challenge. After the induction and challenge applications, the test sites were observed for erythema reactions at 24 and 48 hours following patch removal according to the Buehler scoring scale. DNCB (2,4-dinitrochlorobenzene) served as positive control. For induction 0.4 ml of 0.3 % w/v DNCB in 80 % v/v ethanol in deionized water was used. The challenge was done using 0.4 ml of 0.1 % w/v DNCB in acetone.

Findings: During the induction phase with test-compound, no signs of dermal irritation were noted. The positive control animals displayed moderate to severe signs of skin irritation. Allergic skin reactions did not occur 24 or 48 hours after challenge application in test-compound treated or in negative control animals (Table 5.2.6-1). In all four positive control group moderate signs of allergic skin reactions (erythema) were noted, indicating that the animals were sensitized against DNCB.

Table 5.2.6-1: Closed patch test: Number of animals with signs of allergic skin reactions

Scored after ...	24 h	48 h
Negative control	0/10	0/10
Test group	0/10	0/10
Positive control	4/4	4/4

Conclusion: In a modified Buehler test, there was no evidence that the test compound has sensitizing properties.

5.2.6.2 Maximization test

Report: M. Drew, J. Kerr (1992); XXX-YYYYYY - Skin sensitising effect in guinea pigs (Maximization Test according to Magnusson and Klingman); Organics Inc, unpublished report No.: 21687 (August 21, 1994; report) and 21644A (July 07, 1996; addendum); Organics Inc, Institute of Toxicology, Castlebar, Ireland; dates of experimental work: April 1991 - May 1991.

Guidelines: OECD 406 (equivalent to EEC method B.6 - Directive 92/69/EEC); deviations: none

GLP: Yes (certified laboratory)

Material and methods: Test material: XXX-YYYYYY; Batch FL 921658; purity: 95.6 % [13], in 0.9 % NaCl solution / Cremophor EL (2 % w/v); applied at 0.1 ml/injection intradermally to guinea pigs (BOR:DHPW): 5 % (intradermal application) 6 % (topical application, 1 week after intradermal induction); 0.5 %, 1.0 % (first challenge, 3 weeks after intradermal induction); 0.05 %, 0.1 % (second challenge, 4 weeks after intradermal induction)

Findings: **Range finding for intracutaneous induction:** One guinea pig was injected intradermally with 0.1 ml of the test article as the following concentrations: 0 %, 1 %, 2.5 %, 5 %. The injection sites were assessed after 24 and 48 hours with the following results: 0 % no reaction; 1 % - 5 % grey region with red margin

Range finding for topical induction: 4 concentrations were tested twice on 4 guinea pigs. The results of the treatment for 24 hours under occlusive conditions with 4 dressings soaked in 0.5 ml of the test material are shown in Table 5.2.6.2-1.

Table 5.2.6.2-1: Number of animals exhibiting skin reddening in the range-finding test for topical induction (48 and 72 hours after application)

	6 %		12 %		25 %		50 %	
Hours	48	72	48	72	48	72	48	72
1st test	4	4	4	4	4	4	4	4
	0.5 %		1 %		3 %		6 %	
Hours	48	72	48	72	48	72	48	72
2nd test	0	0	0	0	0	0	4	4

1st and 2nd challenge: Clinical Signs: The treatment was tolerated by all animals - there were no visible effects. The body weight gain of the treatment group of animals corresponded to that of the control groups.

Local findings: After the first challenge, 14 out of 20 test-group animals responded to the 1 % test material while none of 9 control animals showed skin reactions; 5 animals showed a positive response to the 0.5 % concentration. No skin reactions were observed following the second challenge.

Table 5.2.6.2-2: Number of animals exhibiting skin reactions in the maximisation test (48 and 72 hours after initiation of challenge)

	Test substance group				1st and 2nd control group			
	Test patch		Control patch		Test patch		Control patch	
Hours	48	72	48	72	48	72	48	72
1st - 1 %	11	10	0	0	0	0	2	2
1st - 0.5 %	4	2	1	0	0	0	1	1
2nd - 0.1 %	0	0	0	0	0	0	0	0
2nd - 0.05 %	1	0	0	0	0	0	0	0

Following the first challenge x % and x % of the test animals exhibited skin redness to the 1 % and 0.5 % test material concentrations respectively, while none of the control animals reacted. After the 1st challenge xx out of xx test-group animals responded to the 1 % concentration while none of xx control animals showed skin reactions; xx animals exhibited a positive reaction to the 0.5 % concentration.

Conclusion: XXX-YYYYYY has skin sensitizing potential under the conditions of the Maximization Test. Skin sensitization was not provoked following the second challenge.

5.2.7 Summary of acute toxicity:

Table 5.2.7-1: Overview of acute toxicity studies with XXX-YYYYYY

Parameter	Species	Result	Reference
Acute oral LD_{50}	Rat	> 5000 mg/kg	Glaza, 1993c
Acute dermal LD_{50}	Rabbit	> 2000 mg/kg	Glaza, 1993d
Acute inhalation LC_{50} (4 h)	Rat	> 5082 mg/m^3	Hartmann 1993
Acute skin irritation	Rabbit	non irritant	Glaza, 1993a
Acute eye irritation	Rabbit	non irritant	Glaza, 1993b
Skin sensitization - Buehler test	Guinea pig	non-sensitizing	Glaza, 1993e
- Maximization test	Guinea pig	sensitizing	Drew and Kerr, 1992

XXX-YYYYYY is of low toxicity. Slight signs of dermal and ocular irritation were noted after application to the skin and eye of rabbits. In a Buehler type sensitization test, XXX-YYYYYY was found to have no sensitizing potential. In a maximization test according to Magnusson and Klingman one out of twenty animals (5 %) displayed signs of allergic skin reactions.

5.3 Short-term toxicity

5.3.1 Oral 28-day studies

5.3.1.1 Rat

Report: F. Keller, P. Gears (1992): XXXX - Subacute oral toxicity study in rats (feeding study). Organics Inc, unpublished report No. 21644 (August 21, 1994; report) and 21644A (July 07, 1996; addendum); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 407 » EEC B.7.

GLP: yes (certified laboratory).

Deviations: The report was not audited by Quality Assurance. There is no mention of the analysis of the diet to confirm dose levels.

Material and methods: Groups of 10 male and 10 female Wistar rats received XXXX (purity 94.6 %; specification 00 - Document J) in the feed at concentrations of 0, 11, 111 or 111 ppm for 4 weeks. Five male and 5 female animals from each dose group were selected for haematology, clinical chemistry, urinalyses and histopathology. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXXX.

Findings:

General observations: Survival rates were unaffected at levels up to and including 1111 ppm. Female rats exhibited slight transient apathy at 1111 ppm. Food and water intake did not differ significantly from those in controls throughout the entire study. A transient retardation of body weight development occurred in males of the 1111 ppm group (Tab.: 5.3.1.1-1).

Table 5.3.1.1-1: 4-week feeding study in rats: Body weights (g/animal/d)

	0 ppm	11 ppm	111 ppm	1111 ppm
Males				
Day 0	92	93	92	92
Day 6	126	128	124	118 ++
Day 14	171	172	168	157 ++
Day 21	202	204	200	190 +
Day 28/29	232	236	232	221
Females				
Day 0	84	82	84	84
Day 28/29	155	153	159	153

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Table 5.3.1.1-2: 4-week feeding study in rats: Haematology and clinical chemistry

	0 ppm	11 ppm	111 ppm	1111 ppm
Males				
LEUCO [10^9/l]	5.9	7.6	7.6	6.8 +
SEGM [%]	5.2	5.8	6.2	3.5 +
PROT [g/l]	59.0	57.8	58.2	54.8 ++
CHOL [mmol/l]	2.32	2.14	2.22	1.87 ++
Na [mmol/l]	144	144	144	143 +
Females				
CREA [mcmol/l]	50	61	44	39 +
Glucose [mmol/l]	4.75	4.60	4.55	4.18 ++
Na [mmol/l]	144	145	143	142 +

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Haematology, clinical chemistry, urinalysis: Haematology tests afforded no evidence of a treatment-related effect on the red or white blood cell population, or on the haematopoetic organs at levels up to and including 1111 ppm. Leucocyte counts (LEUCO) were elevated, and the numbers of polymorphs (SEGM) were lower in male rats at 1111 ppm. The clinical chemistry of liver tissue showed elevated levels of the cytochrome P-450 mono-oxygenase system (P 450) in male 1111 ppm group rats. In the 1111 ppm group, the males exhibited lower protein (PROT) and cholesterol (CHOL) levels, and the females lower creatinine (CREA) and glucose concentrations. The sodium (Na) levels in both sexes were lower than in the controls (Tab.: 5.3.1.1-2).

Gross pathology, organ weights, histopathology: In the 1111 ppm group, the absolute brain weights were reduced in males, and the relative spleen weights were increased in females. Relative liver weight was elevated in males at 111 ppm and above (Tab.: 5.3.1.1-3). Slight to moderate fatty deposits in the hepatocytes were observed in the livers of male and female rats in the groups treated with doses of 111 ppm and above. The incidence/severity of this finding in the 11 ppm group was not significantly different from that in the controls. Hyperkeratosis of the oesophageal mucosa was observed at 111 ppm and above. In addition one female 1111 ppm group animal exhibited moderate hyperplasia of the urinary bladder epithelium. These findings are regarded as treatment-related effects probably arising fro m the strong irritant properties of XXXX. Ophthalmic examinations afforded no evidence for treatment related changes of the eyes.

Table 5.3.1.1-3: Results of a 4-week feeding study in rats: Organ weights

	0 ppm	11 ppm	111 ppm	1111 ppm
Males				
absolute brain weight [mg]	1734	1711	1753	1674 +
relative liver weight [mg/100g]	4276	4415	4507 ++	4429 +
Females				
relative spleen weight [mg/100g]	211	229	230	243 +

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Conclusion: **No-observed-effect level: 11 ppm; equal to 1.1 mg/kg bw/day (males); 1.1 mg/kg bw/day (females) - based on the histopathology findings (hyperkeratosis of oesophagus mucosa) at 111 ppm**

5.3.1.2 Rat

Report: F. Keller, E. Hagen (1992): XXXX - Subacute oral toxicity in rats. Organics Inc, unpublished report No. 21841(August 21, 1994; report) and 21644A (July 07, 1996; addendum); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 407 » EEC B.7. Deviations: none

GLP: yes (certified laboratory)

Deviations: Histopathology was carried out on 2 male and 2 female rats per dose level only.

Material and methods: In an oral gavage study groups of 10 male and 10 female Wistar rats received XXXX (purity 93.6 %; specification 00 - Document J) at daily doses of 0, 11, 11 or 111 mg/kg bw over a period of 4 weeks. Five male and 5 female animals from each dose group were selected for haematology, clinical chemistry, urinalyses and histopathology.

Findings:

General observations: In all dose-groups clinical symptoms such as salivation, tremor, digging and preening activities were observed after application. These findings and the elevated water intake are regarded to be the result of the local irritant action of XXXX. At 111 mg/kg bw, body weight development was reduced (Table 5.3.1.2-1). Survival rates were unaffected in all dose groups.

Haematology, clinical chemistry, urinalysis: The results of clinicochemical tests with liver tissue indicated an induction of hepatic enzymes. This was manifested by elevated N-demethylase activities (N-DEM) at 111 mg/kg bw/d in males and elevated cytochrome P-450 figures (P 450) at 11 mg/kg bw/d and above in males and at 111 mg/kg bw/d in females. The ASAT and ALAT (males) and SAP (females) activities were higher than in controls at 111 mg/kg bw/d. The ASAT activity in males was also increased at 11 mg/kg bw/d. The albumin levels were depressed in both sexes at 111 mg/kg bw/d. In addition, the males in this group exhibited depressed creatinin levels (CREA). In the females triglyceride (TRIGL) at 11 mg/kg bw/d and above and protein levels (PROT) were reduced (Table 5.3.1.2-2).

Table 5.3.1.2-1: Results of a 4-week gavage study in rats: Body weights (g/animal/d)

	0 mg/kg bw	11 mg/kg bw	11 mg/kg bw	111 mg/kg bw
Males				
Day 0	102	101	99	102
Day 14	179	178	176	155 +
Day 28/29	241	240	243	222 +
Females				
Day 0	93	91	93	93
Day 14	140	141	137	132 ++
Day 28/29	166	177	165	144 +

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Table 5.3.1.2-2: Results of a 4-week gavage study in rats: Clinical chemistry

	0 mg/kg bw	11 mg/kg bw	11 mg/kg bw	111 mg/kg bw
Males				
N-DEM [mU/g]	125.1	151.4	159.9	189.9 ++
P 450 [nmol/g]	41.8	43.8	49.4 ++	57.7 ++
ASAT [U/l]	33.6	39.5	44.4 ++	42.8 +
ALAT [U/l]	33.6	33.8	38.7	48.9 ++
ALBUMIN [g/l]	32.2	31.7	31.2	30.3 +
CREA [mcmol/l]	52	52	49	43 +
Females				
N-DEM [mU/g]	61.8	51.4	57.0	72.1
P 450 [nmol/g]	36.8	35.7	38.8	48.4 ++
SAP [U/l]	238	242	265	297 +
TRIGL [mmol/l]	1.19	0.80 ++	0.85	0.55 +
ALBUMIN [g/l]	35.2	35.1	35.7	32.3 ++
PROT [g/l]	65.9	65.0	66.2	60.8 ++

+ = U-test, 1 % significance level; ++ = U-test, 5 % significance level

Gross pathology, organ weights, histopathology: The elevated relative liver weights determined in animals of the 111 mg/kg bw/d group (Table 5.3.1.2-3) correlated with the results of the clinicochemical tests. In the histopathological examination very slight degenerative effects were seen in hepatocytes of high dose group animals (minimal hepatocellular steatosis in the periportal lobular zones). The other histopathological findings obtained in animals receiving 111 mg/kg bw/d are regarded to be causally related to the strong irritant effect of XXXX on mucosal tissue:

- simple hyperplasia of the urinary bladder epithelium in females;
- hyperkeratosis of the cornifying, multilayer squamous epithelium of the forestomach mucosa in both sexes.

The ophthalmic examinations afforded no evidence for damage to the eyes in the groups treated at doses up to and including 11 mg/kg bw/d. However, the finding that lens fibres were visible in animals receiving 111 mg/kg bw/d is regarded to be treatment-related.

Table 5.3.1.2-3: Results of a 4-week gavage study in rats: Relative organ weights (mg/100 g)

	0 mg/kg bw	11 mg/kg bw	11 mg/kg bw	111 mg/kg bw
Males				
Liver	3900	4086	3972	4322 ++
Spleen	210	233	219	253 ++
Kidneys	658	684	696	743 ++
Testes	1217	1248	1187	1357 ++
Females				
Pituitary	7	5	6	5 +
Adrenals	29	27	30	32 +
Liver	4170	4256	4302	4435 +

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Conclusion: **XXX was tolerated without systemic adverse effects at a dose of 11 mg/kg bw With regard to systemic effects, the NOEL was 11 mg/kg bw/day based on liver enzyme induction at 11 mg/kg bw/day.**

5.3.2 Oral 90-day studies

5.3.3.2 Rat

Report: R. Elbers, E. Hagen (1992a): XXXX - Subchronic toxicity in wistar rats (13-week administration in the diet with a four-week recovery period). Organics Inc, unpublished report No.: 21627 No. (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 408 » FIFRA § 83-1 » 67/548/EEC.

GLP: yes (certified laboratory)

Deviations: T3, T4 and thyroxine in the blood were measured in excess of Guideline requirements. In addition P450 levels in the blood were measured.

Material and methods: Groups of 10 male and 10 female Wistar rats were administered XXXX (purity 93.6 %; specification 00 - Document J) at levels of 0, 11, 111 or 611 ppm in their diet over a period of 13 weeks. Additional recovery groups made up of ten rats of each sex were treated at levels of 0 or 111 ppm over a period of 13 weeks, and then observed for four weeks. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXXX.

Findings:

General observations: At 611 ppm, several animals exhibited a depressed general condition and an ungroomed coat. These findings were reversible.

Figure 5.3.3.2 -1: Results of a 13-week feeding study in rats: Mean Body weights [g] - males

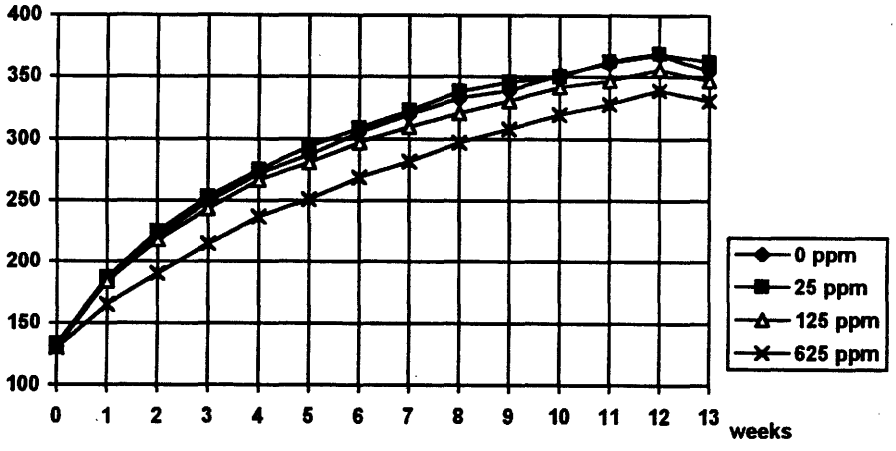
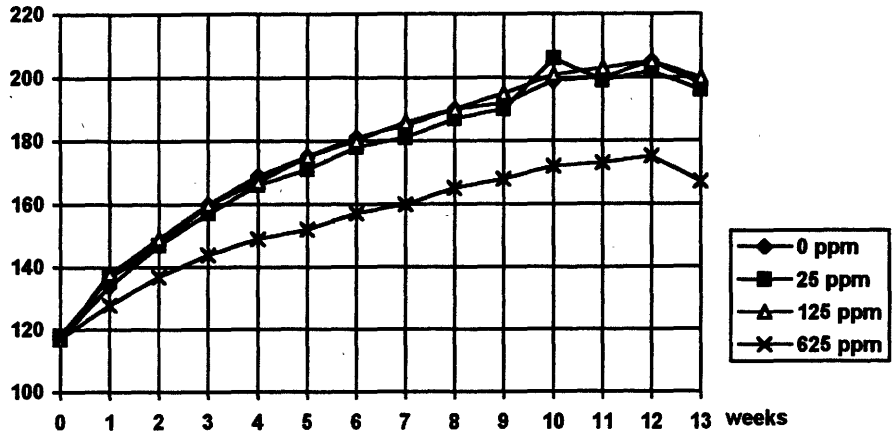


Figure 5.3.3.2 -2: Results of a 13-week feeding study in rats: Mean Body weights [g] - females



The retarded body weight gains observed at the high-dose level were not fully reversible within a post observation period of four weeks (Fig.: 5.3.3.2). Food intake was not affected at levels up to 611 ppm. Animals drank slightly less water at 611 ppm.

Haematology, clinical chemistry, urinalysis: No adverse effects on red and white blood cell numbers were detected at levels up to 611 ppm. Evidence of impaired blood coagulation (transiently lower thrombocyte counts (THRO) and elevated Hepato-Quick readings (HQUICK) could be seen in the high-dose group, but no longer existed following the recovery period. Cytochrome P-450 levels (P 450) in the liver samples from rats treated over a period of 13 weeks showed a statistical significant increase at 111 ppm and above in males. Effects on the liver were observed in high-dose group animals: liver enzyme activities in the serum (aspartate- and alanine-aminotransferase, alkaline phosphatase) were elevated in both sexes. Blood cholesterol (CHOL) levels were depressed to a statistically significant extent in both sexes of the high-dose group. No evidence of disturbances in the kidney function or damage to the kidneys were found at levels up to 611 ppm.

Table 5.3.3.2-1: Results of a 13-week feeding study in rats: Haematology, clinical chemistry

	0 ppm			11 ppm			111 ppm			611 ppm		
Week	**5**	**13**	**17**	**5**	**13**	**17**	**5**	**13**	**17**	**5**	**13**	**17**
Males												
THRO [10^9/l]												
HQUICK [sec]												
P 450 [nmol/g]												
ASAT [U/l]												
ALAT [U/l]												
SAP [U/l]												
CHOL [mmol/l]	2.28	2.46	2.42 re	2.29	2.53		2.32	2.50		1.68 ++	2.00+	1.95 re+
Females												
THRO [10^9/l]												
HQUICK [sec]												
ASAT [U/l]												
ALAT [U/l]												
SAP [U/l]												
CHOL [mmol/l]	2.44	2.14	2.19 re	2.35	2.13		2.20	2.04		1.60 ++	1.51 ++	1.87 re++

re recovery groups; + U-test, 1 %; ++ U-test, 5 %

Table 5.3.3.2-2: Results of a 13-week feeding study in rats: Incidence of treatment related histopathological findings

	0 ppm m / f	11 ppm m / f	111 ppm m / f	611 ppm m / f
BLADDER UROTHEL (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10
- hyperplasia (multifocal)	0 / 0	0 / 0	0 / 0	3 / 4
TONGUE (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10
- hyperkeratosis	0 / 0	0 / 0	0 / 0	7 / 10
OESOPHAGUS (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10
- hyperkeratosis	1 / 0	0 / 0	9 / 5	10 / 10
- hyperplasia/ hypertrophy	1 / 0	0 / 0	9 / 5	10 / 10
FORESTOMACH (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10
- hyperkeratosis	0 / 0	0 / 0	1 / 0	3 / 8
LIVER (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10
- hyaline droplets	0 / 0	0 / 0	0 / 0	3 / 0

Gross pathology, organ weights, histopathology: Slight degenerative liver changes (hyaline droplets) were observed in three of ten males in the high dose group. These effects were no longer manifest or were observed to a lesser degree after 4 weeks recovery. The urinary bladder epithelia of several 611 ppm animals exhibited hyperplastic change. This change turned out to be reversible. Hyperkeratosis in the superficial epithelium was determined in both sexes at 111 ppm and above (in oesophagus and forestomach) and at 611 ppm (in the tongue), and was also accompanied by hyperplastic changes and hypertrophy in the oesophagus of the affected animals. Hyperkeratosis, which also occurred in a few control rats, could no longer be observed, or was only seen at a considerably lower incidence, at the end of the recovery period (Table 5.3.3.2-2). The ophthalmic examinations and histopathology afforded no evidence for oculotoxic effects at 611 ppm.

Conclusion: **NOEL: 11 ppm, equivalent to: 1.1 mg/kg bw/day (males), 1.1 mg/kg bw/day (females), based on histopathological findings in the liver at 111 ppm.**

5.3.2.2 Mouse

Report: R. Elbers, E. Hagen (1992b): XXXX - Subchronic range-finding test for a two-year study in B6C3F1 mice (administration in the diet over a period of about 13 weeks). Organics Inc, unpublished report No.: 21022 (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland. (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 408 » FIFRA § 83-1 » 67/548/EEC

GLP: yes (certified laboratory)

Deviations: none.

Material and methods: Groups of 10 male and 10 female B6C3F1 Mice were administered XXXX (purity 94.6 %; specification 00 - Document J) at levels of 0, 1, 11, 111 or 1111 ppm in their diet over a period of 13 weeks. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXXX.

Findings:

General observations: At 1111 ppm depressed general condition and emaciation, hair loss and ungroomed fur were observed in isolated male mice. In this dose group mice exhibited desiccated or crusted areas of skin at the auricles and/or tail, which on histological examination was shown to represent marked epidermal hyperplasia. Minimal epidermal hyperplasia was also observed in the histology of the auricles in several 111 ppm males. Two males and one female died with causal relationship to the treatment at 1111 ppm. A slightly elevated rate of mortality was noted in both sexes at the high dose. Food and water intakes underwent no significant effect at levels up to 111 ppm. At the high dose, females consumed less food, and males drank more water than the control animals (Table 5.3.2.2-1). The body weight development was not altered to a toxicologically relevant extent at 1 ppm in males, or at levels up to 111 ppm in females. Marginal effects on the weight development were noted in males at 11 and 111 ppm. At the high dose, males and females initially lost weight. As the study progressed, growth in the males was retarded, but was unaffected in females at 1111 ppm.

Table 5.3.2.2-1: Results of a 13-week feeding study in mice: Food intake and water intake

	0 ppm	1 ppm	11 ppm	111 ppm	1111 ppm
Food intake (g/kg bw/d) m	283.7	308.3	311.8	276.4	286.1
f	378.4	366.4	356.5	394.7	323.2
Water intake (g/kg bw/d) m	281.7	298.3	316.2	297.7	385.0
f	331.9	344.7	366.1	367.8	362.5

Haematology, clinical chemistry, urinalysis: Haematology tests performed at the end of the study afforded no evidence of treatment-related effects on the red blood cell population at levels up to 1111 ppm. Leukocyte counts (LEUCO) in both sexes were slightly elevated, but the differential blood count remained unaffected at 1111 ppm. Significantly fewer thrombocytes (THRO) were counted in the high-dose group than in the other groups. The results for urea and cholesterol (CHOL) were situated within the normal physiological range at levels up to 111 ppm, but were elevated (urea) or depressed (cholesterol) to a statistically significant extent at the high dose in both sexes (Table 5.3.2.2-2).

Gross pathology, organ weights, histopathology: Increased centrilobular fatty change of the hepatic lobules (in isolated females at 111 ppm and above), as well as elevated liver weights (Table 5.3.2.2-3) and hepatocellular hypertrophy (both at 1111 ppm) (Table 5.3.2.2-4) were interpreted as evidence of a change in metabolic function in the liver. The epithelium of the urinary bladder and renal pelvis exhibited hyperplastic changes in the 1111 ppm group mice. Effects on the kidneys such as elevated relative kidney weights, increased water intakes and elevated urea levels were found in high dose group animals.

Table 5.3.2.2-2: Results of a 13-week feeding study in mice: Haematology and clinical chemistry

	0 ppm	1 ppm	11 ppm	111 ppm	1111 ppm
Males					
LEUCO [10^9/l]	6.7	5.4	5.8	6.7	8.3
THRO [10^9/l]	1238	1194	1259	1230	1057 ++
UREA [mmol/l]	14.68	15.45	14.89	14.50	20.48 ++
CHOL [mmol/l]	2.90	2.78	2.73	2.67	1.75 ++
Females					
LEUCO [10^9/l]	3.0	3.5	3.8	3.6	5.2 ++
THRO [10^9/l]	1054	1045	1039	1099	950 +
UREA [mmol/l]	8.89	10.01	10.11 ++	9.68	13.70 ++
CHOL [mmol/l]	2.37	2.26	2.29	2.35	1.32 ++

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Table 5.3.2.2-3: Results of a 13-week feeding study in mice: Organ weights

		0 ppm	1 ppm	11 ppm	111 ppm	1111 ppm
LIVER WEIGHT						
Absolute (mg)	m	1440	1364	1338 +	1375	1646 +
	f	1465	1410	1389	1380	1595
Relative (mg/100g)	m	4931	4838	4767	4912	5961 ++
	f	5368	5112	4982+	5205	5927 +
KIDNEY WEIGHT						
Absolute (mg)	m	501	490	499	484	526
	f	433	435	458	421	441
Relative (mg/100g)	m	1714	1737	1775	1729	1908 ++
	f	1591	1580	1640	1586	1639

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Table 5.3.2.2-4: Results of a 13-week feeding study in mice: Incidence of treatment related histopathological findings

	0 ppm m / f	1 ppm m / f	11 ppm m / f	111 ppm m / f	1111 ppm m / f
SKIN (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
- epidermal hyperplasia auricle	0 / 0	0 / 0	0 / 0	6 / 0	9 / 10
- epidermal hyperplasia tail	0 / 0	0 / 0	0 / 0	0 / 0	4 / 9
KIDNEY (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
- epithelial hyperplasia	0 / 0	0 / 0	0 / 0	0 / 0	4 / 7
URINARY BLADDER (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
- Simple hyperplasia	0 / 0	0 / 0	0 / 0	0 / 0	9 / 9
LIVER (no. examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
- hepatocellular hypertrophy	0 / 0	0 / 0	0 / 0	1 / 7	0 / 3
- fatty change	3 / 7	8 / 9	3 / 6	4 / 9	8 / 9
grade 1	3 / 7	8 / 9	3 / 6	3 / 6	8 / 5
grade 2	0 / 0	0 / 0	0 / 0	0 / 3	0 / 3
grade 3	0 / 0	0 / 0	0 / 0	0 / 0	0 / 1

Conclusion: **NOEL: 11 ppm for males, 11 ppm for females, equivalent to 1.1 mg/kg bw/day (males) and 11.1 mg/kg bw/day (females), respectively, based on the morphological liver findings at 111 ppm in females. LOEL (males): 11.1 mg/kg bw/day**

5.3.2.3 Mouse

Report: R. Elbers, E. Hagen, U. Sale (1992): XXXX - Subchronic toxicological study in B6C3F1 mice to examine effects on the skin, kidneys, liver and urinary bladder (thirteen-week administration by gavage and eight-week recovery period). Organics Inc, unpublished report No.: 21330 (August 21, 1994; report) and 21644A (July 07, 1996; addendum); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: 67/548/EEC.

GLP: yes (certified laboratory)

Deviations: The study methodology conformed to the current guideline requirements for subchronic toxicity testing. The main deviations were: the number of animals was only 5 per dose group; organ weights were not determined..

Material and methods: Groups of five male and five female B6C3F1 mice were administered 0, 11, 111 or 1111 mg/kg bw doses of XXXX (purity 93.6 %; specification 00 - Document J) by gavage over a period of 13 weeks. Five additional animals of each sex were included in the 0, 111 and 1111 mg/kg groups, and following the 13-week treatment period were left untreated for observation over an eight-week recovery period.

Findings:

General observations: No treatment-related clinical signs were observed at doses up to 111 mg/kg bw/d. High-dose mice exhibited extension spasms shortly after treatment. The body weight development, mortality, and food and water intakes underwent no significant effect over the examined range of doses.

Haematology, clinical chemistry, urinalysis: Depressed cholesterol levels were determined in the male and female 1111 mg/kg bw/d group animals during the 13th week, but could not be statistically verified due to the small numbers of animals. No significant deviations in this parameter were apparent at the end of the recovery period. Induction of microsomal mono-oxygenases in the liver (7-ethoxycoumarin deethylase (EOD); 7-ethoxyresorufin deethylase (ERD); aldrin epoxidase (ALD); epoxide hydrolase (EH); glutathione-S-transferase (GSH-T); UDP-glucuronyl transferase (GLU-T) were noted in all treatment groups. Morphological evidence for liver stress (hepatocellular hypertrophy and reduced glycogen levels) was found at 111 mg/kg bw/d and above. In addition, single-cell necroses also occurred at 1111 mg/kg bw/d, and lower cholesterol levels (CHOL) were determined in the plasma (Table 5.3.2.3-1).

Gross pathology, histopathology: Urinary tract epithelial hyperplasia was detected in the bladders of the 180 and 1111 mg/kg bw/d dose group mice. Mice in the high-dose group exhibited hyperplastic changes in the epidermis of the auricles and (males only) tails (Tab.: 5.3.2.3-2). The effects on the liver, urinary bladder and epidermis described, were found to be reversible.

Table 5.3.2.3-1: Results of a 13-week gavage study in mice: Clinical chemistry

	0 mg/kg bw	11 mg/kg bw	111 mg/kg bw	1111 mg/kg bw
Males				
CHOL [mmol/l]				
- main group	3.61	3.29	3.25	2.53
- recovery group	3.28	–	3.05	2.96
EOD [nmol/g/min]				
- main group	13.0	19.4	28.9	30.5
- recovery group	15.2	–	–	16.6
EOR [nmol/g/min]				
- main group	0.81	1.59	1.82	1.35
- recovery group	2.05	–	–	1.53
ALD [nmol/g/min]				
- main group	32.8	109.7	156.4	115.8
- recovery group	42.0	–	–	41.8
GSH-T [µmol/g/min]	295.8	267.6	332.0	323.9
GLU-T [nmol/g/min]	54	63	74	74
Females				
CHOL [mmol/l]				
- main group	2.71	2.66	2.49	2.13
- recovery group	2.36	–	2.48	2.44
EOD [nmol/g/min]				
- main group	23.5	18.8	38.7	31.8
- recovery group	21.4	–	–	23.6
EOR [nmol/g/min]				
- main group	1.27	1.17	2.84	2.15
- recovery group	1.67	–	–	1.39
ALD [nmol/g/min]				
- main group	74.2	82.9	239.7	216.8
- recovery group	41.2	–	–	46.6
GSH-T [µmol/g/min]	137.5	128.9	151.1	150.0
GLU-T [nmol/g/min]	88	99	79	68

Table 5.3.2.3-2: Results of a 13-week feeding study in mice: Incidence of treatment related histopathological findings

	0 mg/kg bw m / f	11 mg/kg bw m / f	111 mg/kg bw m / f	1111 mg/kg bw m / f
SKIN (no. examined)	5 / 5	5 / 5	5 / 5	5 / 5
- epidermal hyperplasia ears	0 / 0	0 / 0	0 / 0	3 / 1
- epidermal hyperplasia tail	0 / 0	0 / 0	0 / 0	2 / 0
STOMACH (no. examined)	5 / 5	5 / 5	5 / 5	5 / 5
- hyperceratosis	0 / 0	0 / 0	1 / 0	3 / 3
URINARY BLADDER (no. examined)	5 / 5	5 / 5	5 / 5	5 / 5
- Simple hyperplasia	0 / 0	0 / 0	1 / 0	4 / 1
LIVER (no. examined)	5 / 5	5 / 5	5 / 5	5 / 5
- hepatocellular hypertrophy	0 / 0	0 / 0	1 / 0	3 / 0
- single cell necrosis	0 / 0	0 / 0	0 / 0	1 / 1
- glycogen reduced	1 / 1	0 / 0	4 / 2	5 / 3

Conclusion: **NOAEL: 11 mg/kg bw. As evidence of liver enzyme induction was seen in all treatment groups, the no-observed effect level was < 11 mg/kg bw/day. This dose can be regarded as a no-observed adverse effect level.**

5.3.2.4 Dog

Report: R. Jones, L. Elcock (1994): XXXX - 13-Week subchronic feeding study in beagle dogs. Organics Inc, unpublished report No.: MR7442 (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 409 » FIFRA § 82-1 » 87/302/EEC, Part B.

GLP: yes (certified laboratory)

Deviations: The dogs were not of a defined breed and differed considerably in body weight..

Material and methods: XXXX (purity 93.5 - 94.9%; specification 00 - Document J) was administered in the diet to Beagle dogs at nominal concentrations of 0, 11, 111 and 1111 ppm for thirteen weeks. Four animals per sex and dose level were used. In order of increasing doses the treated dogs ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXXX.

Findings:

General observations: There was no difference with regard to body weight gain and feed consumption between treated and control groups. Only incidental clinical signs were observed, none of which were considered treatment-related. There were no treatment-related ophthalmological findings.

Haematology, clinical chemistry, urinalysis: The following changes in clinical pathology parameters at 1111 ppm were considered to be compound-related (Table 5.3.2.4-1):

- decreased albumin levels (both sexes),
- increased alkaline phosphatase levels (females),
- decreased triglyceride levels (females).

Table 5.3.2.4-1: Results of a 13-week feeding study in dogs: Clinical chemistry

	0 ppm	11 ppm	111 ppm	1111 ppm
Males				
Albumin [g/dL]	3.3	3.2	3.2	2.6 *
Females				
Albumin [g/dL]	3.3	3.2	2.9 *	2.6 *
SAP [u/l]	64	70	89	168 *
Triglycerides [mg/dL]	59	61	52	46 *

Anova + Students t-tests (two-sided): * $p \leq 5$ %

Gross pathology, organ weights, histopathology: Statistical significant increases in the relative liver weight were evident in the 111 and in 1111 ppm males and the 1111 ppm females (Table 5.3.2.4-2). Microscopic observation of minimal diffuse hepatocytomegaly (111 & 1111 ppm males, and 1111 ppm females) also suggested that the liver was the target organ (Table 5.3.2.4-3).

Table 5.3.2.4-2: Results of a 13-week feeding study in dogs: Organ weights

	0 ppm	11 ppm	111 ppm	1111 ppm
LIVER WEIGHT				
Relative (mg/100g) m	2.827	3.056	3.749 *	3.645 *
f	2.969	2.906	3.204	3.791 *

Anova + Students t-tests (two-sided): * $p \leq 5$ %

Table 5.3.2.4-3: Results of a 13-week feeding study in dogs: Incidence of histopathological findings

	0 ppm m / f	11 ppm m / f	111 ppm m / f	1111 ppm m / f
LIVER (no. examined)	4 / 4	4 / 4	1 / 4	4 / 4
- hepathocytomegaly	0 / 0	0 / 0	2 / 0	4# / 4#

= significantly different from control ($p \leq 0.05$)

Conclusion: **No-observed-effect level: 11 ppm; equal to 0.11 mg/kg bw/day (males); 0.11 mg/kg bw/day (females) - based on the findings at 111 ppm in males (increased relative liver weight)**

5.3.3 Other routes

5.3.3.1 Subacute inhalation studies on rats

Report: J. Parker (1992): XXXX Aerosol - Subacute inhalation toxicity in the rat according to OECD Guideline No. 412. Organics Inc, unpublished report No.: 21785 (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 412 » FIFRA § 82-4 » EEC B.8.

GLP: yes (certified laboratory)

Deviations: The exposure time was 1 hour a day for 5 days per week only. Test conditions and exposure data were not reported in detail.

Material and methods: Groups of 10 male and 10 female Wistar rats were exposed to XXXX aerosol concentrations (purity 95.3%; specification 00 - Document J) of 1.1, 11.1 or 111.1 mg/m^3 air (mean content, analytically determined) under dynamic conditions for one hour per day, five days per week over a period of four weeks. The aerosol exhibited particle characteristics rendering it respirable to the rat in all groups. The technique corresponded to head nose-only exposure. Rats exposed to conditioned air or to an aerosol of the vehicle (blend of polyethylene glycol 400 and ethanol) under identical test conditions were used as control animals.

Findings:

Physical parameters - test atmosphere: The results show that exposure conditions which met the standards for stability and exhibited the necessary degree of reproducibility existed throughout the exposure period.

Table 5.3.3.1-1: Results of a 4-week inhalation study on rat: Physical parameters - test atmosphere

Nominal concentration (mg PE/ m^3 air	0 [air]	0 [veh.]	1.1	11.1	111.1
Aerosol concentrations (mg/m^3 air)	0	0	1.1	11.1	1111.1

[air] = air control group; [veh.] = vehicle control group

General observations: Rats exposed to levels of 1.1 and 11.1 mg/m^3 air tolerated the treatment without test substance-induced clinical symptoms or mortality. No evidence of neurological changes was observed (reflex tests). A toxicologically significant effect on rectal temperature was observed, as were effects on body weight gain. Rats exposed to a level of 111.1 mg/m^3 air exhibited ungroomed fur and decreased motility during exposure weeks zero and one. Clinical symptoms could be observed starting at the beginning of exposure week two (among others: staggering gait, decreased motility, narrowed palpebral fissure, hypersalivation, ungroomed fur and piloerection, reddened conjunctivae, reddened and bloody rhinal zone, transient breathing sounds, abnormal digging and preening activities and an upright tail). Local dermal reactions, particularly at the less densely haired at the test substance aerosol contact sites, were predominant near the end of the study. The ophthalmic examinations afforded evidence for test substance-induced corneal damage in this group. No evidence of a change in reflex pattern was observed. Rectal temperature was depressed in the rats exposed to 111.1 mg/m^3 air. A summary of the results obtained are provided in Table 5.3.3.1-2.

Table 5.3.3.1-2: Results of a 4-week inhalation study on rat: Rectal temperatures

mg/m^3	0 [air]	0 [veh.]	1.1	11.1	111.1
	Rectal temperatures [°C] - males				
Day 0	37.6	37.2	37.2	37.4	37.2
Day 7	37.9	38.1	37.5	37.8	36.1 +
Day 21	37.9	37.4	37.6	37.6	36.1 +
	Rectal temperatures [°C] - females				
Day 0	37.0	36.3	37.2	37.4	36.1
Day 7	38.0	37.5	38.1	37.9	36.2 +
Day 21	38.4	38.0	37.9	37.9	36.0 +

Haematology: Examination of the differential diagnostically significant haematology parameters showed an increase in the blood coagulation time (H-Quick), depressed thrombocyte (THRO) and elevated leukocyte counts (LEU) in the 111.1 mg/m^3 air group animals. The differential blood count exhibited a relative increase in the polymorphonuclear granulocyte fraction (SEGM) and a relative decrease in the lymphocyte fraction (LYM) at levels of 11.1 mg/m^3 air and above. These effects are regarded as causally related to the inflammatory changes which occurred in the skin areas. Marginal decreases in the haemoglobin level (HGB) and hematocrit (HCT) reading were determined in female animals at levels of 11.1 mg/m^3 air and above. With respect to changes in the haematology, a level of 1.1 mg/m^3 air was tolerated without effect. The results are listed in Table 5.3.3.1-3.

Clinical chemistry: An effect on specific blood parameters was observed, particularly in the 111.1 mg/m^3 air group rats, in the clinical chemistry blood tests performed at the end of the study: elevated serum ALAT and ASAT activities, depressed plasma cholinesterase activity (CHE, females only), reduced total protein (PROT) and albumin levels, and an increase in the globulin fraction (GLOB) and relative reduction in the albumin fraction in protein electrophoresis. The cholesterol level (CHOL) underwent concentration-related reduction at levels of 11.1 mg/m^3 air and above. Evidence for a significant change in the N-demethylase/O-demethylase (N-DEM/O-DEM) or cytochrome P-450 activities (P 450) was only found in the

111.1 mg/m^3 air group (N-DEM/P-450 depressed in males, not affected to a toxicologically significant extent in females; O-DEM slightly elevated in males and females). The results are listed in Table 5.3.3.1-4.

Table 5.3.3.1-3: Results of a 4-week inhalation study on rat: Haematological parameters

mg/m³	0 [air]	0 [veh.]	1.1	11.1	111.1
Males					
HQUICK [sec]	33.1	33.8	32.9	34.5	37.1 ++
LEU [10E9/l]	6.4	6.0	6.0	5.1	8.1
THRO [10E9/l]	918	986	896	983	831
SEGM [%]	8.3	9.6	10.1	13.0 ++	28.8 ++
LYM [%]	87.5	85.1	86.8	84.0 +	67.6 ++
HGB [g/l.]	146	154 +	150	144	138
HCT [l/l]	0.479	0.497	0.485	0.468	0.448 +
Females					
HQUICK [sec]	29.7	30.3	30.6	28.9	33.7 ++
LEU [10E9/l]	3.8	4.6	5.6	4.1	6.5 +
THRO [10E9/l]	951	1052	1027	908	777 ++
SEGM [%]	8.4	9.5	9.9	12.2	27.4 ++
LYM [%]	88.0	88.0	86.8	85.4	69.9 ++
HGB [g/l.]	140	139	145	131 +	127 +
HCT [l/l]	0.446	0.443	0.471	0.425	0.415

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Table 5.3.3.1-4: Results of a 4-week inhalation study on rat: Clinical chemistry parameters

mg/m³	0 [air]	0 [veh.]	1.1	11.1	111.1
Males					
ASAT [U/l]	51.6	57.4	54.1	56.2	75.4 ++
ALAT [U/l]	43.9	47.0	46.0	45.4	84.4 ++
ALBUMIN [g/l]	31.7	32.4	31.7	31.0	27.6 ++
N-DEM [mU/g]	121.5	130.9	119.0	121.5	94.8 ++
P450 [nmol/g]	40.5	39.9	41.4	42.1	31.2 ++
Females					
ASAT (GOT) [U/l]	62.9	57.2	56.4	52.9	88.4 ++
ALAT (GPT) [U/l]	39.6	43.2	41.6	45.3	86.1 ++
ALBUMIN [g/l]	31.8	33.3	31.8	32.5	25.7 ++
CHE [kU/l]	1.66	1.78	1.71	1.47	0.78 ++
O-DEM [mU/g]	10.2	9.7	11.1	11.3	13.4 ++
N-DEM [mU/g]	78.7	67.4	63.5	69.0	88.5
P450 [nmol/g]	32.3	32.1	34.8	35.3	31.7

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Urinalysis: Elevated levels of proteins (PROT), bilirubin (BILI), ketone bodies (KETO), ammonium-magnesium (triple) phosphate and corpuscular components were observed in the 111.1 mg/m^3 air group animals. A concentration-related increase in the triple phosphate level was present in female rats at levels of 11.1 mg/m^3 air and above. The results are listed in Table 5.3.3.1-5.

Table 5.3.3.1-5: Results of a 4-week inhalation study on rat: Urinalysis

mg/m³	0 [air]	0 [veh.]	1.1	11.1	111.1
Males					
PROT (GRADE 3)	1/10	0/10	0/10	0/10	6/10 +
BILI (GRADE 1)	2/10	0/10	0/10	0/10	9/10 ++
KETO (GRADE 1)	6/10	7/10	3/10	1/10	10/10 +
Females					
PROT (GRADE 3)	0/10	0/10	0/10	0/10	6/10 ++
BILI (GRADE 1)	0/10	0/10	0/10	0/10	8/10 ++
KETO (GRADE 1)	1/10	0/10	0/10	0/10	6/10 +

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Organ weights: Toxicologically and statistically significant changes in the organ-to-body weight relationship occurred in rats exposed to 111.1 mg/m^3 air. A large reduction in thymus weight was observed in both males and females. In males only, a marginal reduction in heart and spleen weights was reported. A toxicologically significant increase in liver and kidney weights was observed in the female animals of this group. The results are listed in Table 5.3.3.1-6.

Table 5.3.3.1-6: Results of a 4-week inhalation study on rat: Absolute organ weights

mg/m³	0 [air]	0 [veh.]	1.1	11.1	111.1
Males					
Thymus	308	290	338	268	94 ++
Heart	824	826	858	788	723 ++
Spleen	460	398	464	422	301 ++
Females					
Liver	5399	5625	5740	5593	6341 +
Thymus	204	194	204	206	73 ++

+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Pathology: On histopathological examination of the 111.1 mg/m^3 air group, squamous epithelial metaplasia in the nasal cavity was observed, as well as epithelial hyperplasia and hyperkeratosis in the larynx zone. An elevated rate of bronchiolo-alveolar proliferation with an increase in alveolar macrophages was noted in the lungs, and hyperkeratosis in the oesophagus. The eyes exhibited corneal hyperplasia, and the eyelids hyperplasia accompanied by hyperkeratosis. The severest local dermal lesions - hyperkeratosis, epithelial hyperplasia, and extended inflammatory infiltration and scab - were found in the muzzle zone. Hyperkeratosis and epithelial hyperplasia were also seen in the mamma zone and on the tail. The male animals exhibited atrophic thymus changes which are considered to represent a secondary stress-related effect. The urinary bladder urothelium exhibited hyperplastic lesions in the 111.1 mg/m^3 air group animals. The results are listed in Table 5.3.3.1-7.

Table 5.3.3.1-7: Results of a 4-week inhalation study on rat: Incidence of histopathological findings

mg/m³ Sex	0 [air] m / f	0 [veh.] m / f	1.1 m / f	11.1 m / f	111.1 m / f
EYES AND EYELIDS (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
corneal hyperplasia	0 / 0	0 / 0	0 / 0	0 / 1	4 / 4
eyelid hyperplasia	0 / 0	0 / 0	0 / 0	0 / 0	9+/ 9+
eyelid hyperkeratosis	0 / 0	0 / 0	0 / 0	0 / 0	10+/10+
NASAL / PARANASAL CAVITIES (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
squamous-cell hyperplasia	1 / 4	1 / 5	2 / 2	3 / 4	8+/ 3
goblet-cell hyperplasia	0 / 4	3 / 5	4 / 4	2 / 5	2 / 5
hyperaemia	6 / 8	7 / 7	3 / 5	8 / 7	5 / 4
LARYNX (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
hyperplasia	0 / 0	0 / 0	0 / 1	3 / 2	7+/ 8+
hyperkeratosis	0 / 0	0 / 0	0 / 1	2 / 2	7+/ 7+
round-cell infiltration	0 / 1	0 / 0	0 / 2	0 / 1	6+/ 5
LUNGS (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
hyperaemia	4 / 5	7 / 8	6 / 7	8 / 5	8 / 9
bronch./alveol. prolif.	0 / 0	1 / 0	0 / 0	0 / 0	7+/ 2
thickening of septa	1 / 0	1 / 0	1 / 1	0 / 3	8+ / 1
OESOPHAGUS (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
hyperkeratosis	0 / 0	0 / 0	0 / 0	0 / 0	2 / 8+
LIVER (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
hyperaemia	2 / 4	3 / 6	3 / 2	2 / 5	8+/ 7
vacuolation hepatocytes	0 / 6	5+ / 1	2 / 4	5+/ 1	9+/ 5
MESENTERIAL LYMPH NODES (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
sinus catarrh	3 / 6	3 / 2	9+ / 5	7 / 4	10+/ 4
BLADDER (no. of animals examined)	10 / 10	10 / 10	10 / 10	10 / 10	10 / 10
hyperplasia	0 / 0	0 / 0	0 / 0	0 / 0	4 / 5+

\+ U-test, 1 % significance level; ++ U-test, 5 % significance level

Conclusions: **NOEC: 11.1 mg/m³ air; equivalent to approx. 1.1 mg XXXX/kg bw/exposure day, based on haematology and clinical chemistry effects at 11 mg/m³ air (increase in the polymorphonuclear granulocyte fraction, haemoglobin, haematocrit, cholesterol)**

A subchronic inhalation study is not necessary, since the 28-day study showed low toxicity based mainly on local effects. Furthermore the vapour pressure is < 10^{-2} Pa.

5.3.3.2 Subacute dermal study on rabbits

Report: H. Voss, M. Rink (1995): XXXX - Subacute dermal toxicity in the rabbit. Organics Inc, unpublished report No.: 23710 (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).

Guidelines: OECD 410 » FIFRA § 82-2 » EEC B.9.

GLP: yes (certified laboratory)

Deviations: The test groups each consisted of 3 animals/sex with intact skin and 3 animals/sex with abraded skin.

Material and methods: The local and systemic tolerance of XXXX (purity 95.5 %; specification 00 - Document J) was examined in a subacute dermal toxicity study on rabbits. The test substance was formulated with Cremophor EL (2% v/v) in sterile physiological saline solution. The animals were treated with the test compound in doses of 0, 0.1, 1 and 11 mg/kg bw for 6 hours per day over a period of 3 weeks (the corresponding concentrations were: 0, 0.011, 0.01 and 0.11 %). Five males and 5 females were used per group. A satellite group (1 mg/kg bw) and a further control group were observed over a 14-day post-treatment phase to test for any lasting or reversible toxic effects.

Findings:

The appearance, behaviour, feed consumption and body weights of the dose animals corresponded to those of the control animals. There were no mortalities. Skin erythema occurred in nearly all animals in the test substance groups (Table 5.3.3.2-1).

Table 5.3.3.2-1: Results of a subacute dermal study in rabbits: Mean degree of skin erythema

DOSE [mg/kg]	sex	day 1	day 10	day 20	day 21
0	m	0	0	0	0
0.1	m	0	0.4	0.4	0.4
1	m	0	0.6	1.0	0.8
11	m	0	3.7	3.7	3.3
0	f	0	0	0	0
0.1	f	0	0.2	0.2	0.2
1	f	0	1.0	0.6	0.8
11	f	0.1	3.5	3.9	3.6

Other findings such as scales, swelling, hardening and cracking occurred among all animals in the highest dose group, in some females in the mid-range dose group and in one male in the lowest dose group. Skin fold thickness was significantly increased among both sexes at the highest dose and among the females at the mid-range dose. No treatment-related haematological or clinical chemistry effects occurred. No treatment-related changes to the examined organs were observed in terms of gross pathological, gravimetric or histopathological findings.

The following histopathological changes of the skin were observed in all treated animals:

- diffuse epidermal hyperplasia,
- focal epidermal hyperplasia,
- hyperkeratosis,
- inflammation reaction.

These effects were mainly reversible at the end of the post-treatment period.

Table 5.3.3.2-2: Incidence of local skin findings

Local skin findings *	0 mg (n = 10)		0.1 mg (n = 5)		1 mg (n = 5)		11 mg (n = 10)	
	M	F	M	F	M	F	M	F
Scaly in places			1			2	10	10
Scaly						1	6	6
Slightly swollen							10	9
Swollen in places								1
Swollen							10	8
Cracked in places						1	9	8
Cracked							3	2
Hardened in places							2	4
Hardened							3	5

* where a finding occurs more than once during the course of the study (also each summarised finding where an incidence greater than N = 5 is possible), it is only shown once per animal in the incidence table.

Table 5.3.3.2-3: Mean skin fold thickness [mm]

DOSE [mg/kg]	sex	0	6	13	20
0	m	2.74	2.74	2.93	3.17
0.1	m	3.14	3.16	3.04	3.38
1	m	2.78	2.94	3.18	3.62
11	m	3.07	3.17	3.52	5.38
0	f	2.21	2.31	2.26	2.34
0.1	f	2.16	2.32	2.48	2.78
1	f	2.12	2.24	2.44	3.00
11	f	2.37	2.51	2.90	4.50

Conclusion: **NOEL: systemic: > 11 mg/kg bw/day**
local: < 1.1 mg/kg bw/day

5.3.4 Summary of short-term toxicity studies

Type of study	Animal species	Dose range tested	NOEL	Reference
oral, 4 weeks	rat	0, 11, 111 or 111 ppm, equivalent to 0, 1.1, 11.1 and 11.1 mg/kg bw in males and to 0, 1.1, 11.1 and 11.1 mg/kg bw in females	**11 ppm**	Keller and Gears (1992)
oral, 4 weeks	rat	0, 11, 11 or 11 mg/kg bw	**11 mg/kg bw**	Keller and Hagen (1992)
oral, 13 weeks	rat	0, 11, 111 or 111 ppm equivalent to 0, 1.1, 11.1 and 11.1 mg/kg bw in males and to 0, 1.1, 11.1 and 11.1 mg/kg bw in females	**11 ppm**	Elbers and Hagen (1992a)
oral, 13 weeks	mouse	0, 11, 11, 111 or 1111 ppm	**11 ppm**	Elbers and Hagen (1992b)
oral, 13 weeks	mouse	0, 11, 111 or 111 mg/kg bw	**11 mg/kg bw**	Elbers *et al.* (1992
oral, 13 weeks	dog	0, 11, 111 and 1111 ppm equivalent to 0, 0.1, 1.1 and 11.1 mg/kg bw in males and to 0, 0.1, 1.1 and 11.1 mg/kg bw in females	**11 ppm**	Jones and Elcock (1994)
inhalation, 4 weeks	rat	11.1, 11.1 or 111.1 mg/m^3 air	**11.1 mg/m^3 air**	Parker (1992)
dermal, 3 weeks	rabbit	0, 0.1, 1 and 1 mg/kg bw/day	**local: 0.1, systemic: 1 mg/kg bw/day**	Voss and Rink (1995)

Following repeated oral administration of high doses of XXXX, no evidence for cumulative toxicity was seen in rats, mice and dogs. A daily dose of 111 mg/kg bw (which is equivalent to about 1/6 of the LD_{50}) was tolerated in a 4-week study by rats without increased mortality. In rodents unspecified clinical signs such as reduced body weight development, reduced feed intake and poor general condition were observed.

In the three species investigated, the liver was the main target organ. In the mouse signs of liver enzyme induction occurred at doses of 111 mg/kg bw/day. At higher doses hypertrophy of hepatocytes, degenerative alterations (single cell necrosis, centrilobular fat deposition) and liver weight increase were seen. Fatty changes of hepatocytes were found in the rat and the dog together with an increase of transaminases activity in the serum. Investigation using recovery groups have shown that the liver effects were reversible following cessation of compound administration.

No systemic toxicological effects occurred in rabbits following daily dermal application of 11 mg/kg bw/day over a period of 3 weeks.

As in the case of oral administration, the liver was a target organ following subacute inhalation. 11.1 mg/m^3 air was a clear no-observed effect concentration.

5.4 Genotoxicity testing

PART 4

Section 4 Format for the Presentation of Residue Date in Summary Form (Annex II, Point 6)

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

1 Suggested format for the presentation of GAP information

Crop	Country	Formulation type (code) and content of active substance (g/kg)	Application				PHI, days
			Method	Rate kg as/ha	Spray conc, kg as/hL	Number	
Barley	France			1.5			21
Beans	Greece	WP 500	foliar	0.6-1.5	0.1-0.25	3-4	7
Beans	Portugal	WP 500	foliar		0.13	1-2	7
Beans, green	Spain	WP 500	foliar	1.6	0.16		21
Brassica vegetables	Italy	WP 500	foliar	0.35-0.40			10
Lettuce	France [1]	WP 500	foliar	0.64			21-41[2]
Lettuce	Israel[3]	WP 500	foliar	2.0		weekly	11

[1] g: glasshouse use. [2] Summer PHI 21 days, winter PHI 41 days [3] proposed registration.

Notes: 1 Remarks can be added as footnotes, as in the example

2 Suggested abbreviations for footnotes to the GAP table

a	aerial application	pr	proposed registration
fg	field and glasshouse use	st	seed treatment
g	glasshouse use only	t	table grapes only
gs	growth stage restriction	w	wine grapes only
Po	post-harvest use		

3 Application rates should be reported using the following units:

field treatment	kg as/ha
grain treatment, post-harvest	g as/t
furrow treatment	g as/m
space fumigation	g as/m^3
spray concentration	kg as/hL

2 Suggested Format for the Presentation of Residue Data

CROP country, year	Application				Portion Analyzed	Residues, mg/kg after PHI days					Reference
	Formulation (type and content of as)	No	kg as/ha	kg as/hL		0	4	7	14	21	
BROCOLLI											
Germany,1976											PBH360/77
Netherlands, 1980											RL401-90NL
CABBAGES, HEAD											
Canada, 1986											8013.86a
Germany, 1978											PBJ287/78

Notes: 1 Include individual residue results in as far as is possible. If results are grouped avoid wide ranges. If there are a number of values at the same level they can be recorded as <0.05 (7), where there are 7 values of < 0.05 mg/kg.

2 Underline residues resulting from treatments within GAP, but wherever such underlining is used its meaning must be explained in a footnote, a note in the table caption, or a note in the introduction to the tables.

3 Round numbers in tables to a practical level, usually 2 significant figures. A formulation concentration should be reported as 250 g as/kg, not 250.00 g as/kg. Residues should be reported as 0.36 and 4.5 mg/kg, not 0.363 and 4.47 mg/kg.

4 Near the LOQ (limit of quantification - determination) rounding to 1 significant figure is recommended. For example, if the LOQ is 0.05 mg/kg, report residue data from 0.05 to 0.09 mg/kg to 1 significant figure.

3 Alternative Format for the Presentation of Residue Data - where metabolite levels are also reported

CROP Country, year	Application				Residues, mg/kg			Reference
	Formulation (type and content of as)	No	kg as/ha	kg as/hL	PHI	Parent compound	Metabolite	
BROCCOLI								
Germany, 1976					0 4 7 14 21			PBH360/77
Netherlands, 1980					0 4 7 14 21			RL401-90NL
CABBAGES, HEAD								
Canada, 1986					0 4 7 14 21			8013.86a
Germany, 1978					0 4 7 14 21			PBJ287/78

PART 5

Section 5 Fate and Behaviour in the Environment (Annex II, Point 7)

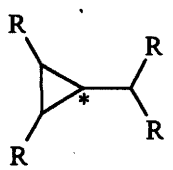
The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

7.1 Fate and behaviour in soil

The fate and behaviour of XXXX in soils was investigated using [cyclopropyl-1-^{14}C]-labelled compound - radiochemical purity > 99 %, specific radioactivity 1.11 MBq/mg (Specification 00 - Document J).

* indicates position of label



7.1.1 Route and rate of degradation

7.1.1.1 Route of degradation

7.1.1.1.1 Aerobic degradation

Report: Schulz, K. (1995b): Aerobic degradation of XXXX in soil. Organics Inc, unpublished report No. 98476

Guideline: BBA-Guidelines for the Testing of Plant Protection Products in Registration Procedures, Part IV, 4-1 (December 1986), no deviations.

GLP: yes (certified laboratory)

Report: Schulz, K. (1995d): Aerobic degradation and metabolism of XXXX in soil. Organics Inc, unpublished report No. 92564

Guideline: BBA-Guidelines for the Testing of Plant Protection Products in Registration Procedures, Part IV, 4-1 (December 1986), no deviations.

GLP: yes (certified laboratory)

Test System: The metabolism of [cyclopropyl-1-^{14}C]XXXX was investigated in 4 soils in accordance with the BBA Guidelines. In one study (Schulz, 1995d) 3 soils were used (silt loam, 2 sandy loams), whilst in a further study (Schulz, 1995b) a loamy sand was used. The soil characteristics are summarized in Table 7.1.1.1.1-1. In all cases, the concentration of test substance used, corresponded to the maximum field application rate of 700 g as/ha, assuming 100 % soil interception and a soil depth of 10 cm. The incubation conditions were: aerobic; dark; 40 % max. water holding capacity (exc. Howe Indiana; 48 %); and temperature 20 ± 2 °C.

Table 7.1.1.1.1-1: Soils used to investigate degradation and metabolism of XXXX

Soil designation Origin Soil type	1 Location 1 Hamburg (D) silt loam	2 Location 2 Kent (UK) sandy loam	3 Location 3 Indiana (USA) sandy loam	4 Location 4 Mainz (D) loamy sand
Textural analysis (USDA)				
2000 - 50 µm, sand	36.9 %	58.2 %	65.5 %	83.0 %
< 50 - 2 µm, silt	51.1 %	31.0 %	26.3 %	13.0 %
< 2 µm, clay	12.0 %	10.8 %	8.2 %	4.0 %
pH value Water	8.1	6.5	7.1	6.3
$CaCl_2$, 0.01 N	7.3	6.3	6.8	5.5
Organic C	0.9 %	1.98 %	1.09 %	2.15 %
Cation exchange capacity (meq/100 g)	10.0	10.0	10.0	10.0
Particle density (g/ml)	2.55	2.45	2.54	2.46
40 % of maximum water holding capacity (g H_20 for 100 g dry soil)	13.1 g	16.6 g	11.3 g	17.67 g
Microbial biomass (mg microbial carbon/kg soil)	307	246	285	256
Reference	Schulz, 1995d			Schulz, 1995b

Findings: The results obtained, in terms of distribution of radioactivity and metabolites at different sampling dates are summarized in Table 7.1.1.1.1-2. Average total recoveries were high throughout, ranging from 99-101 %. The amount of radioactivity bound to soil increased during the early part of the experiment. In most cases binding attained a maximum after 30 days, and decreased towards the end of the study. However, in the case of loamy sand soil, the initial increase in bound residues was slower. XXXX was both degraded in the soil and bound to the soil during the period of incubation. In view of the fact that in 3 out of 4 soils, the bound residue reached a maximum after 30 days of incubation, it is evident that the bound residue was bio-available for degradation (mineralization) by micro-organisms.

The results obtained in these laboratory studies indicated that aerobic metabolism of [cyclopropyl-1-^{14}C]XXXX proceeds via different pathways. Six metabolites (including CO_2) were identified. All the metabolites (excluding CO_2) occurred at levels lower than 9 % of the applied radioactivity (< 0.06 mg metabolite/kg soil) at all time intervals. The ultimate degradation product was carbon dioxide which accounted for 20-40 % of the applied radioactivity after 100 days.

Table 7.1.1.1.1-2: Recovery of radioactivity in % and distribution of metabolites after application of [cyclo-propyl-1-^{14}C]XXXX to soil

Soil	Days after appl.	$^{14}CO_2$ (%)	Vol. org. com-pounds (%)	XXXX (%)	M1 xxxxx (%)	M2 xxxx (%)	M3 xx (%)	M6 (%)	M11 (%)	Bound resi-dues (%)	Paper filter (%)	Un-known (%)	Total (%)
1	0	-	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
	1	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
	3	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
	7	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	1.1	99.9
	14	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
	30	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	1.1	99.9
	60	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
	100	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	1.1	11.1	1.1	-	99.9
2	0	-	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	1	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	3	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	7	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	14	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	30	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	60	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	100	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
3	0	-	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	1	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	3	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	7	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	14	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	30	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	60	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
	100	11.1	<0.1	11.1	1.1	1.1	-	-	-	11.1	1.1	*	99.9
4	0	-	<0.1	11.1	-	-	-	-	-	1.1	1.1	*	99.9
	1	11.1	<0.1	11.1	1.1	-	1.1	-	-	1.1	1.1	*	99.9
	3	11.1	<0.1	11.1	1.1	1.1	1.1	-	-	1.1	1.1	*	99.9
	7	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	-	11.1	1.1	*	99.9
	14	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	-	11.1	1.1	*	99.9
	30	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	-	11.1	1.1	*	99.9
	60	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	-	11.1	1.1	*	99.9
	100	11.1	<0.1	11.1	1.1	1.1	1.1	1.1	-	11.1	1.1	*	99.9

* analysis of as and main metabolites only

Report: Schulz, K. (1994): Leaching behaviour of XXXX aged in soils. Organics Inc, unpublished report No. 63489

Guideline: BBA: Versickerungsverhalten von Pflanzenschutmitteln (4-2) 1986, Teil IV. Deviations: during irrigation, leaching columns (A, B from the application rate 700 g as/ha, soil from location 1) became partly blocked (both on day 32). Irrigation continued for 23 days (7 days for the first 200 ml). Consequently, a study with a third column was performed using the irrigation time of 2 days specified. The soil sample originally set aside for the determination of microbial biomass at the end of the study, was instead used for a leaching experiment.

GLP: yes (certified laboratory)

Test System: Information on the degradation of XXXX was derived from a study on leaching behaviour of the compound aged in soils using [cyclopropyl-1-^{14}C]XXXX. Three soils were used: loamy sand, location 1; sand, location 2; silty loam, location 3. The soil characteristics are summarized in Table 7.1.1.1.1-3. The concentration of test substance corresponded to either 350 g as/ha (loamy sand and silty loam) or 700 g as/ha (sand), assuming 100 % soil interception and a soil depth of about 4 cm. The incubation conditions were as follows: aerobic; dark; 40 % water holding capacity; a temperature of 20 ± 1°C.

Table 7.1.1.1.1-3: ***Recovery of radioactivity and distribution of metabolites after application of [cyclopropyl-1-^{14}C]XXXX to soil and incubation under aerobic conditions (for codes of metabolites see Figure 7.1.1.1)***

Soil Details	Location 1			Location 2			Location 3		
Batch	SP 149			SP 1121			-		
clay (%)	5.3			0.1			11.0		
silt (%)	8.8			10.5			52.5		
sand (%)	85.9			89.4			36.5		
pH	6.0			6.1			7.0		
Org C (%)	0.54			0.57			1.08		
Microb. Bio. mg C/kg	81			84			310		
Application rate (as)	73.6 µg/100 g soil			146.7 µg/100 g soil			73.7 µg/100 g soil		
Ageing days	0	30	62	0	32	60	0	30	62
% Applied radioactivity		1.1							
$^{14}CO_2$			11.1		11.1	11.1		11.1	11.1
XXXX	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
Metabolite 1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Metabolite 2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Metabolite 3	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Metabolite 6		1.1	0.1		1.1	1.1		1.1	1.1
Metabolite 11		1.1	0.1		1.1	1.1		1.1	1.1
Metabolite 12		1.1	0.1		1.1	1.1		1.1	1.1
Metabolite 15			0.1	1.1					1.1
unknown			0.1			1.1			1.1
bound residues	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
paper filter	1.1	1.1	1.0	1.1	1.1	1.1	1.1	1.1	1.1
Total	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9

Findings: Results obtained, in terms of distribution of radioactivity and metabolites after ageing periods of 0 days, 1 and 2 months are presented in Table 7.1.1.1.1-3. Average total recoveries ranged from 99.9 - 101 %. In the case of each of the soils tested, the level of bound residue increased with time, and by day 60 to 62, had reached 11.1 - 22.2 %.

The metabolic profile observed, was essentially similar to that established in the aerobic degradation studies reported earlier in this section, however two additional trace metabolites were identified and quantified.

Report: Bird, K. (1995): (Cyclopropyl-1-^{14}C)XXXX residues in following crops. Organics Inc, unpublished report No. 65489

Guideline: SETAC - Procedures for assessing the environmental fate and ecotoxicity of pesticides

GLP: yes (certified laboratory)

Test System: Further information on the metabolism of XXXX in soil can be derived from the controlled rotational crop study reported. Residues in following crops were investigated following application of [cyclopropyl-1-^{14}C]XXXX formulated as a SC 400, to the surface of a sandy loam soil at an application rate equivalent to 1.4 kg as/ha. The proposed maximum annual rate of application is 1.1 kg as/ha. Swiss chard, turnips and wheat were sown after ageing periods of 30 days (1st interval) and 161 days (2nd interval) following application. Each crop was harvested at maturity. Soil samples were taken at days 0, 30 and 161 following application.

Findings: The findings are summarized in Table 7.1.1.1.1-4. Total residues in the 0-15 cm soil layer amounted to 1.11 mg/kg on day 0, 0.11 mg/kg on day 30 and 0.01 mg/kg on day 161. Residues consisted mainly of unchanged parent compound although some metabolites were present in low concentrations (at any one time less than 7 % of the radioactivity in the soil). The occurrence of tertbutylketone is an artefact resulting from soil extraction with hot acetonitrile.

Table 7.1.1.1.1-4: ***Distribution of metabolites after application of [cyclopropyl-1-^{14}C]XXXX to a sandy loam soil in a controlled rotational crop study (for codes of metabolites see Figure 7.1.1.1)***

Metabolite/ Fraction	Days after application			
	30		161	
	%	mg/kg	%	mg/kg
XXXX	1.1	1.11	1.1	1.11
Metabolite 1	1.1	1.11	1.1	1.11
Metabolite 2	1.1	1.11	1.1	1.11
Artefacts and unknown metabolites	1.1	1.11	1.1	1.11
Solids	1.1	1.11	1.1	1.11
Total	100.0	1.11	100.0	1.11

7.1.1.1.2 Supplementary studies

7.1.1.1.2.1 Anaerobic degradation

Given the proposed usage pattern for XXXX, as a fungicide for post-emergence application in the form of a spray to cereal crops, it is suggested that an anaerobic soil degradation study is not required. Information on the degradation of XXXX in aquatic systems is included at point 7.2.1.3.2.

7.1.1.1.2.2 Soil photolysis

Report: Bond, B. (1995b): Photolysis of XXXX on soil surfaces (according to the EPA guidelines). Organics Inc, unpublished report No. 36544

Guidelines: US EPA Guidelines, § 161-3: Photodegradation Studies on soil. Deviations: none.

GLP: yes (certified laboratory)

Test System: The photodegradation of XXXX was studied on thin layers of the Californian loam soil "X Ranch". The test material was [cyclopropyl-1-^{14}C]XXXX at a concentration of about 11.1 µg/g soil (dry weight). This equates to a field rate of *ca* 2.0 kg as/ha, *i.e.* greater than maximum recommended dose rate. The thin layers of soil were continuously irradiated with a Xenon lamp for the duration of the test period - 11 days. The temperature of the test system was maintained at 25 ± 1 °C. The water content of samples was adjusted to 75 % of the 1/3 bar moisture of the soil. Duplicate samples were taken for analysis at 0, 3, 7, 10 and 11 days after treatment.

Findings: Under the experimental conditions used, XXXX degraded with an experimental half-life (DT_{50}) of 9.9 days. A total of eight degradation products was observed in the soil extracts along with the parent compound. XXXX was degraded throughout the course of the experiment. The major metabolites were found to be Metabolite 1, Metabolite 2, Metabolite 3 and Metabolite 4. Each of them accounted for far less than 10 % of the applied radioactivity. Those metabolites appear in the proposed metabolic pathway for XXXX in soil, as presented in Figure 7.1.1.1.

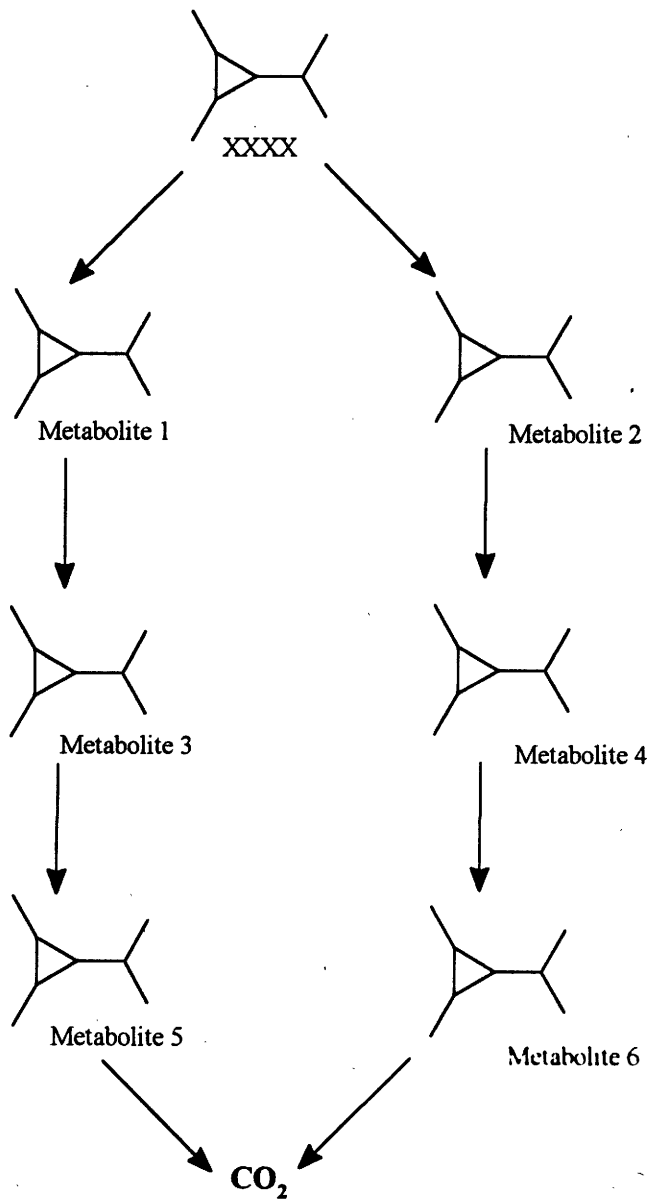
Metabolite 3 was possibly in equilibrium with as and/or it was an intermediate to the 1- or 2- metabolites. During the test period of 11 days an amount equivalent to 1.1 % of the applied radioactivity was degraded to carbon dioxide in both the irradiated as well as the dark samples. The amount of non-extracted radioactivity slightly increased to the end of the experiment and reached 11.1 % of the applied radiocarbon in the irradiated samples and 11.1 % in the dark samples. Recovery ranged from 99.0 to 101.1 % of the applied radioactivity. Degradation of XXXX observed in the dark samples was slower than in the irradiated samples.

Route of degradation - summary and conclusions

The following are the reactions that are believed to be involved in the breakdown of XXXX in soils:-

- desalkylation of the parent compound (formation of Metabolite 1 and Metabolite 2)
- oxidation of the parent compound (formation of Metabolite 3)
- hydrolysis of the parent compound and metabolites (formation of Metabolite 4)
- ring cleavage followed by formation of CO_2

Figure 7.1.1.1: Metabolism of XXXX in soil



Proposed definition of the residue of relevance for the environment

On the basis of the studies and data presented in this section, it is evident that the parent compound only is the relevant residue for quantification in soil.

7.1.1.2 Rate of degradation

7.1.1.2.1 Laboratory studies

Report: Schulz, K. (1995b): Aerobic degradation of XXXX in soil. Organics Inc, unpublished report No. 98476

Guideline: BBA-Guidelines for the Testing of Plant Protection Products in Registration Procedures, Part IV, 4-1 (December 1986). Deviations: none

GLP: yes (certified laboratory)

Report: Schulz, K. (1995d): Aerobic degradation and metabolism of XXXX in soil. Organics Inc, unpublished report No. 92564

Guideline: BBA-Guidelines for the Testing of Plant Protection Products in Registration Procedures, Part IV, 4-1 (December 1986). Deviations: none.

GLP: yes (certified laboratory)

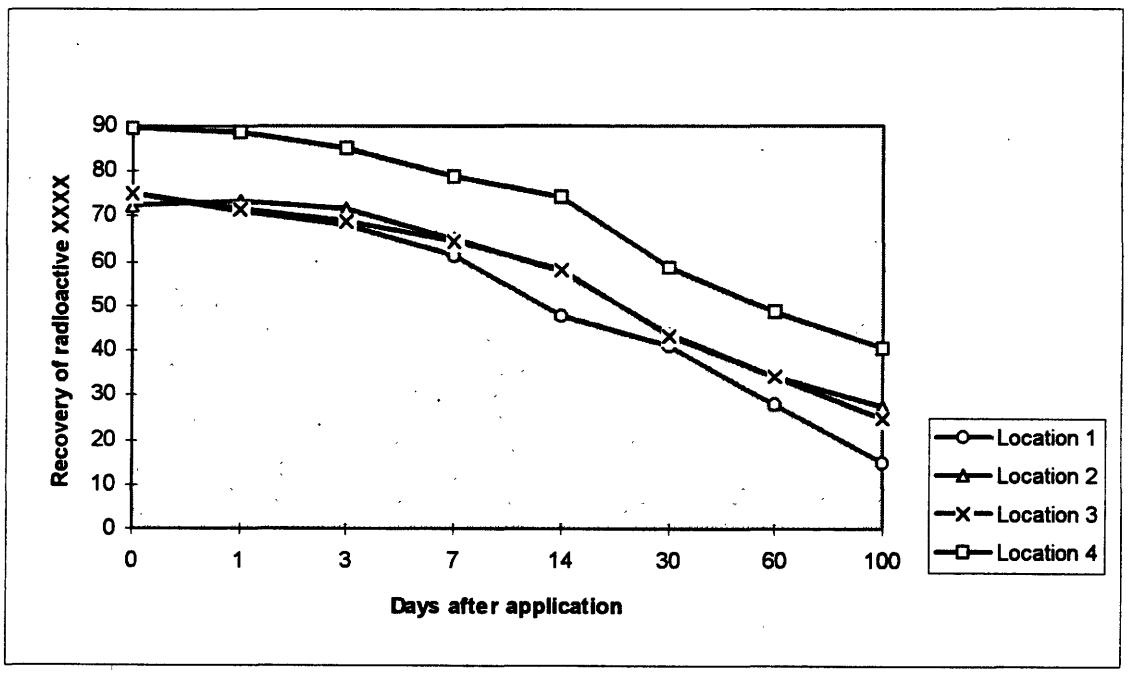
Findings: A summary of the results obtained on the rate of chemical and biological degradation of XXXXX in soil under laboratory conditions, for a number of soils, is provided in Table 7.1.1.2.1 and Figure 7.1.1.2.1. In all cases the studies reported relate to aerobic degradation. The amounts of test material used were equivalent to the maximum field rate of 700 g as/ha, assuming 100 % soil interception and a soil depth of 10 cm. Under the test conditions, the DT_{50} values were to range from 33-44 days. The shortest half-life was obtained from the soil with the highest biomass value. Since the DT_{90} was not reached within the incubation period of 100 days, an estimation was not made as to the disappearance time of 90 % of the applied compound.

The degradation of XXXX at lower temperature is covered by field experiments in the area of Northern Europe (see 7.1.1.2.2).

Table 7.1.1.2.1: Summary of laboratory studies on aerobic degradation of [cyclopropyl-1-^{14}C]XXXX in four soils (dark conditions, temp. 18 to 22 °C)

Report	Soil			DT_{50} in days TLC System	Remark
	Source	Type (sand %)	% Org. C		
Schulz, 1995d	Location 1	silt loam (36.9)	0.9	33	1.5th Order
	Location 2	sandy loam (58.2)	1.98	33	2nd Order
	Location 3	sandy loam (66.5)	1.09	44	2nd Order
Schulz, 1995b	Location 4	loamy sand (83.0)	2.15	44	Sqrt 1st Order

Figure 7.1.1.2.1: Aerobic degradation of [cyclopropyl-1-^{14}C]XXXX, in four soils, in the dark, at 18 to 22 °C



7.1.1.2.2 Field studies

Report: Winter, H. (1995a): Dissipation of XXXX in soils under field conditions. Organics Inc, unpublished report No. 2078

Guidelines: BBA Guideline, part IV, 4-1 (1986). Deviations: none.

GLP: yes (certified laboratory)

Report: Winter, H. (1995b): Dissipation of XXXX in soils under field conditions. Organics Inc, unpublished report No. 2002

Guidelines: BBA Guideline, part IV, 4-1 (1986). Deviations: none.

GLP: yes (certified laboratory)

Report: Winter, H. (1995c): Field rotational crop study with XXXX 500 EC in Germany and Great Britain. Organics Inc, unpublished report No. 2120

Guidelines: BBA Guideline IV, 3-10 (1988), ECPA Guideline (1993). Deviations: none.

GLP: yes (certified laboratory)

Report: Winter, H. (1995d): Dissipation of XXXX in soils under field conditions. Organics Inc, unpublished report No. 2132

Guidelines: BBA Guideline, part IV, 4-1 (1986). Deviations: none.

GLP: yes (certified laboratory)

Test System: A number of field studies have been performed in Northern Europe (Germany, UK and France) to investigate degradation and dissipation of XXXX in soil and to determine the concentrations of Metabolite 1 and Metabolite 2 in soil under conditions relevant to commercial usage (Winter, 1995a, b, d). These trials were performed using the formulated product XXXX SC 400 (containing 402.2 g of XXXX per litre). Soils at 6 of the locations did not have vegetation cover while the soils at 8 locations did have vegetation cover.

Findings: The results obtained are presented in summary form in Table 7.1.1.2.2-1. Information derived from field rotational crop studies (4 sites; Winter 1995c) has also been included. In trials performed without vegetation (bare soil), application of 0.7 kg as/ha in the spring period resulted in DT_{50} values for XXXX ranging from 11 to 11 days. DT_{90} values for XXXX determined in bare soil studies, ranged from 111 to 111 days. In trials performed with vegetation, application of 0.7 and 1.4 (two trials) kg as/ha in the spring period resulted in DT_{50} values for XXXX ranging from 11 to 11 days. DT_{90} values for XXXX determined in studies with vegetation, ranged from 111 to 111 days. On the basis of these results it can be concluded that rates of dissipation of XXXX in cropped and bare soil are essentially similar, however, there was some evidence to suggest that dissipation rates were faster with vegetation.

Following application of XXXX, residue concentrations declined with time. Starting from an application rate of 700 g XXXX/ha and a soil density of 1.5 g/cm³ a theoretical XXXX concentration of 0.5 mg as/kg was evenly disturbed in the 0-10 cm soil layer. Within 111 to 222 days residues of XXXX declined to between < 0.005 and 0.05 mg/kg (0.005 mg/kg = limit of determination). Taking account of the highest remaining residue, about 90 % of the applied XXXX was degraded within a growing season. Concentrations of the corresponding metabolites 1 and 2 declined to an amount of 0.01 and 0.01 mg/kg, respectively, at the end of the experimental period.

Although not designed to address the rate of degradation in soil, the results obtained in field crop rotational studies, confirmed the fairly rapid rate of degradation of XXXX.

Taking into account the relatively low concentrations remaining in soil after a growing season, the absence of phytotoxic effects even at higher concentrations and the lack of leaching potential into deeper soil layers, a soil accumulation study is not necessary.

Table 7.1.1.2.2-1: Field dissipation of XXXX (as SC 400 formulation) in Northern Europe

Reference	Soil source	Cropping situation	Appl rate as/ha	Soil type	Soil properties		Statistical Evaluation XXXX		
					Organic carbon %	pH	DT_{50} (days)	DT_{90} (days)	Function
Winter, 1995a	Location 1, UK	cropped soil	0.7	Sandy loam	1.14	7.5	11	111	Sqrt 1.5th order
	Location 2, UK	cropped soil	0.7	Loamy sand	0.88	7.3	11	111	Sqrt 1.5th order
	Location 3, Germany	bare soil	0.7	Silt loam	0.97	6.5	11	111	Sqrt 1st order
	Location 4, Germany	cropped soil	0.7	Loam	1.08	6.8	11	111	2nd order
Winter, 1995b	Location 4, Germany	bare soil	0.7	Silt loam	0.87	6.4	11	111	2nd order
	Location 3, Germany	bare soil	0.7	Sandy loam	1.21	6.6	11	111	Sqrt 1st order
	Location 5, Germany	bare soil	0.7	Sandy loam	1.27	5.9	11	111	Sqrt 2nd order
	Location 6, Germany	bare soil	0.7	Silt loam	1.00	6.7	11	111	Sqrt 1st order
	Location 7, Germany	bare soil	0.7	Silty clay loam	1.40	7.8	11	111	Sqrt 1st order
Winter, 1995d	Location 1, UK	cropped soil	1.4	Sandy loam	1.08	7.4	11	111	Sqrt 2nd order
	Location 2, UK	cropped soil	1.4	Sandy loam	1.88	7.0	11	111	Sqrt 1st order
	Location 1, UK	cropped soil	0.7	Sandy loam	1.08	7.4	11	111	Sqrt 2nd order
	Location 2, UK	cropped soil	0.7	Sandy loam	1.88	7.0	11	111	Sqrt 1st order
	Location 1, France	cropped soil	0.7	Silt loam	1.29	7.2	11	111	Sqrt 1st order

7.1.1.2.3 Storage stability of soil residues

Report: Winter, H. (1995e): Storage stability of XXXX. Organics Inc, unpublished report No. 747/95

Guidelines: No official guideline available

GLP: yes (certified laboratory)

Test System: XXXX and the metabolites 1 and 2 were applied to soil at 400 µg/kg. The treated soil samples were stored at a temperature below -18 °C. After 364 days the samples were analyzed using the methods 00111 and 00222 (Winter, 1994a, b - cross references 4.2.2 /01 and 4.2.2 /02).

Findings: The results obtained demonstrate that there is no significant degradation of XXXX and the metabolites 1 and 2 in soil over a period of one year during storage below -18 °C:-

	Recovered amounts (%)	
Days after treatment	0	364
XXXX	100.1	99.9
Metabolite 1	100.1	99.9
Metabolite 2	100.1	99.9

7.1.2 Adsorption and desorption

Report: Bond, B (1995a): Adsorption/desorption of XXXX in soil. Organics Inc, unpublished report No.: 27566

Guidelines: US EPA-guideline § 163-1 of October 18, 1982. Deviations: none.

GLP: yes (certified laboratory)

Test System: Adsorption and desorption of XXXX was measured using a batch equilibrium procedure (based on EPA Guideline § 163-1) to determine the Kd and Koc values of [cyclopropyl-1-^{14}C]XXXX in five soils, including one subsoil. Details of the soils used are provided in Table 7.1.2.

Findings: A summary of the results obtained can be found in Table 7.1.2. The adsorption process for XXXX, in the concentration range studied (0.01-5 mg as/ml), can be described with a high degree of accuracy using the Freundlich equation. The adsorption constants Kd calculated from the Freundlich isotherms for the five test soils range from 1.11 to 11.11. Koc values of 111-1111 were obtained.

The percentage adsorption of parent compound varied between 11.1 and 11.1 % of the applied as depending on soil type and concentration. A single desorption determination with 0.01 M $CaCl_2$ solution resulted in 1.1-11 % of absorbed as being desorbed. The calculated desorption Kd values obtained ranged from 1.11 to 11.11, with corresponding Koc values of 1111 to 1111.

Table 7.1.2: Adsorption and Desorption of [cyclopropyl-1-^{14}C] XXXX on a range of soils

Soil Reference	Soil Type	Org. C (%)	Adsorption			Desorption		
			Kd (ml/g)	1/n	Koc (ml/g)	Kd (ml/g)	1/n	Koc (ml/g)
Location 1, 0-30 cm horizon	loamy sand	1.8	11.11	0.1111	111	11.11	0.1111	1111
Location 1, 30 - 60 cm horizon	loamy sand	0.3	11.11	0.1111	1111	1.11	0.1111	1111
Location 2	silt loam	2.4	11.11	0.1111	1111	11.11	0.1111	1111
Location 3	silty clay	0.64	11.11	0.1111	1111	11.11	0.1111	1111
BBA 2.1	sand	0.7	11.11	0.1111	111	1.11	0.1111	1111

Conclusion: **On the basis of these findings XXXX should be classified as being of low mobility to immobile.**

7.1.3 Mobility in soil

7.1.3.1 Column leaching studies

In the light of the findings reported in under point 7.1.2 with respect to absorption and desorption characteristics of XXXX, column leaching studies are not required.

7.1.3.2 Aged residue column leaching

Report: Schulz, K. (1994): Leaching behaviour of XXXX aged in soils. Organics Inc, unpublished report No.: 63489

Guidelines: BBA: Versickerungsverhalten von Pflanzenschutmitteln (4-2) 1986 Teil IV. Deviations: during irrigation, leaching columns (A, B from the application rate 700 g as/ha, soil from location 1) became partly blocked (both on day 32). Irrigation continued for 23 days (7 days for the first 200 ml). Consequently, a study with a third column was performed using the irrigation time of 2 days specified. The soil sample originally set aside for the determination of microbial biomass at the end of the study, was instead used for a leaching experiment.

GLP: yes (certified laboratory)

Test System: The leaching characteristics of aged [cyclopropyl-1-^{14}C]XXXX was studied using three soils: Location 1: loamy sand, location 2: sand, location 3: silty loam. Details of the soil characteristics are included in Table 7.1.1.1.1-1. Soil samples containing labelled XXXX (at rates equivalent to 350 and 700 g as/ha, the latter being the maximum field rate) were incubated in the dark for 0, 30-33 and 60-62 days at a temperature of 20 ± 1°C, at 40 % water holding capacity. After ageing the incubated soil was packed on top of a column (inner diameter 5 cm) containing fresh soil. Water was applied to simulate rainfall (300 ml in two days). The leachate was collected in two fractions of about 180 ml each.

Findings: The results obtained for all tests are summarised in Table 7.1.3.2.

Table 7.1.3.2: Leaching behaviour of [cyclopropyl-1-^{14}C]XXXX in soil (Values in % of applied radioactivity, except "Total residue" and "µg as/leachate")

Applied amount Soil (type)	350 g/ha as Location 1 (loamy sand)				700 g/ha as Location 2 (sand)					350 g/ha as Location 3 (silty loam)			
Ageing (days)	30		62		32		33	60		30		62	
Individual test	A	B	A	B	A	B	C	A	B	A	B	A	B
1. Volatile compounds	**1.1**	**1.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**
$^{14}CO_2$	1.1	1.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
2. Soil (total)	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**	**11.1**
Segment I	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
extract	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
as	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1
Segment II	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Segment III	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
3. **Leachate** (total as and ≥ 5 metabolites)	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**
Total residue (µg)	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	.11	1.11	1.11	1.11
Fraction a	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
Fraction b	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
as	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
µg as/leachate (200 ml)	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
Σ (1-3) Total	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**

XXXX and its metabolites displayed a very limited leaching capacity. Following overhead irrigation, segments II and III of the soil columns contained 1-11 % of the applied radioactivity. Almost all the total radioactivity still present, remained in the upper soil segment. The upper segments were processed separately and were found to contain 11-11 % (Location 1) and 11-11 % (Location 3) parent compound, respectively. The radioactivity in segment II (< 5 %) was somewhat higher in the experiment with the higher application rate but the radioactivities in segments III were nearly identical (< 1 % after 60 days).

APPENDIX 8

FORMAT FOR THE COMPILATION OF *TIER II* SUMMARIES - ANNEX III

PART 1

Section 1 **Identity of the Plant Protection Product; Physical, Chemical and Technical Properties of the Plant Protection Product; Data on Application; Further Information on the Plant Protection Product; Proposals including Justification of the Proposals for the Classification and Labelling of the Plant Protection Product; Proposals for Risk and Safety Phrases in Accordance with Article 16 (1) (g) and (h) and the Proposed Label (Annex III, points 1 to 4 and 12)**

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

---

1 ***Identity of the plant protection product***

1.1	**Applicant:**	name and address	Person to contact:	xxxxxxxxx xxxxxxxxxx
			Telephone No	1111 1111 1111111
			Telefax No	1111 1111 1111111
1.2	**Manufacturer:**	name and address	Contact point - as applicant	
	Location of plant:	name and address	Person to contact:	xxxxxxxxx xxxxxxxxxx
			Telephone No	1111 1111111
			Telefax No	1111 1111 1111111
	Manufacturer of the active ingredient:		name and address	
			Person to contact:	xxxxxxxxx xxxxxxxxxx
			Telephone No	1111 1111 1111111
			Telefax No	1111 1111 1111111
1.3	**Trade name:**		XXXX1	
	Manufacturer's code number:		0122915 (development number)	
1.4	**Composition of the preparation**			
	Identity of active substance		XXXX	
	CAS, EU and CIPAC numbers:		CAS: 111111-11-1	CIPAC: not allocated
			EINECS: not allocated	ELINCS: not allocated

Content of active substance

content of pure active substance: 400 g/L XXXX (declared)

content of technical active substance: 431.9 g/L XXXX technical

at a typical purity of the technical as of 94 %.

Identity and content of formulants: refer to file of confidential information provided separately (Document J)

1.5 **Physical state:** liquid : suspension concentrate [Code: SC]

1.6 **Function** fungicide

2 ***Physical, chemical and technical properties of the plant protection product***

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Colour and physical state (IIIA 2.1)						
Odour (IIIA 2.1)						
Explosive properties (IIIA 2.2.1)						
Oxidizing properties (IIIA 2.2.2)						
Flash point (IIIA 2.3)						
Flammability (IIIA 2.3)						
Auto-flammability (IIIA 2.3)						
Acidity or alkalinity and pH (IIIA 2.4.1)						
pH of a 1 % aqueous dilution, emulsion or dispersion (IIIA 2.4.2)						

Appendix 8 **Format for the Compilation of *Tier II* Summaries - Annex III** **Part 1** **Section 1**

Company name **Month and year** **Active Substance (Name)** **page of**

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Kinematic viscosity (IIIA 2.5.1)						
Viscosity (IIIA 2.5.2)						
Surface tension (IIIA 2.5.3)						
Relative density (IIIA 2.6.1)						
Bulk or tap density (IIIA 2.6.2)						
Storage stability after 14 days at 54 °C (IIIA 2.7.1)						
Stability after storage for other periods and at other temperatures (IIIA 2.7.1)						
Minimum content after heat stability testing (IIIA 2.7.1)						
Effect of low temperatures on stability (IIIA 2.7.2)						
Ambient temperature shelf life (IIIA 2.7.3)						
Wettability (IIIA 2.8.1)						
Persistence of foaming (IIIA 2.8.2)						
Suspensibility (IIIA 2.8.3)						
Spontaneity of dispersion (IIIA 2.8.3)						

Appendix 8 **Format for the Compilation of *Tier II* Summaries - Annex III** **Part 1** **Section 1**

Company name **Month and year** **Active Substance (Name)** **page of**

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Dilution stability (IIIA 2.8.4)						
Dry sieve test (IIIA 2.8.5)						
Wet sieve test (IIIA 2.8.5)						
Particle size distribution - nominal size range of granules (IIIA 2.8.6.1)						
Dust content and particle size of dust (IIIA 2.8.6.2)						
Friabilty and attrition (IIIA 2.8.6.3)						
Emulsifiability, emulsion stability and re-emulsifiability (IIIA 2.8.7.1)						
Stability of dilute emulsions (IIIA 2.8.7.2)						
Flowability (IIIA 2.8.8.1)						
Pourability (including rinsed residue) (IIIA 2.8.8.2)						
Dustability following accelerated storage (IIIA 2.8.8.3)						
Physical compatibility of tank mixes (IIIA 2.9.1)						
Chemical compatibility of tank mixes (IIIA 2.9.1)						

Test or Study & Annex point	Guideline and method	Test material purity and specification	Findings	Comments	GLP Y/N	Reference
Adhesion to seeds (IIIA 2.10)						
Distribution in seed (IIIA 2.10)						

2.11 Summary and evaluation of data presented under points 2.1 to 2.10

XXXX 400 SC is not explosive, oxidising, or flammable. Its pH is within the range that occurs naturally *e.g.* in soil. Its stability allows storage under practical and normal commercial conditions. Its technical properties indicate that no particular problems are to be expected, when it is used as recommended.

3 *Data on application*

3.1 Field of use: agriculture

3.2 Nature of the effects on harmful organisms: fungicidal
XXXX is absorbed to a limited degree in plants and is translocated in the apoplast

3.3 Details of intended use

Crop	Crop code	Disease	Disease code
Barley, spring and winter	HORVS, HORVW	Rhynchosporium secalis	RHYNSE
Winter wheat	TRZAW	Septoria tritici	SEPTTR

3.4 Rate of application per unit treated, in terms of g or kg of preparation and active substance

1.5 L product /ha= 0.6 kg as/ha

3.5 Concentration of active substance in material used (diluted spray) in g/L

1.5 - 3 g/L (1.5 L product = 0.6 kg as. in 200 - 400 L water /ha)

3.6 Description of the method of application, type of equipment used and type and volume of diluent per unit of area or volume

Spray application with standard tractor mounted hydraulic field sprayers, water volume 200 - 400 L/ha

3.7 Maximum number of applications and their timing

2 applications first application: at appearance of disease,
last application: in barley at the beginning of flowering (GS 61)
in wheat at the end of flowering (GS 69)

For each application, growth stages of the crop or plants to be protected:	For the first application the crop stage is not important, for the last application see above
For each application, development stages of the harmful organism concerned:	At appearance of disease
Duration of protection afforded by each application:	3 - 6 weeks depending on disease pressure
Duration of protection afforded by the maximum number of applications:	6 - 12 weeks depending on disease pressure
3.8 Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops	No waiting period needed
Limitations on choice of succeeding crops, if any	No limitations
3.9 Proposed instructions for use as printed or to be printed, on labels:	Provided - see document C

4 *Further information on the plant protection product*

4.1.1 Description and specification of the packaging and materials used in packaging, size, capacity, size of openings, types of closure and seals

1 L bottle:	Material:	HDPE-COEX with barrier of E/VAL or PA alternative: HDPE bottle
	Shape/size:	Round / 88.5 x 234
	Opening:	42 mm diameter
	Closure:	Screw cap with additional tamper evident, *e.g.* sealing disk

5 L container:	Material:	HDPE alternative: HDPE-COEX with barrier of E/VAL or PA
	Shape/size:	Square / 194 x 112 x 362, handle isolated from the content
	Opening:	54.7 mm diameter (GIFAP 63)
	Closure:	Screw cap with additional tamper evident, *e.g.* sealing disk

4.1.2 Suitability of the packaging and closures

Strength, leakproofness, resistance to normal transport and handling

Test results: Satisfactory (ADR)

UN registration Nos.	1 litre bottle	xxxxxx (10 x 1 L),
		xxxxxx (20 x 1 L)
	5 litre container	xxxxxx (4 x 5 L)

4.1.3 Resistance of the packaging material to its contents

The material proposed for use is known from experience to be very resistant to influences of chemicals: product odours from such container have never developed with any of our products; the material used in its construction is not permeable to solvents - including aromatic hydrocarbons; reactions of the product with oxygen are avoided by replacing all remaining air in the container with nitrogen before closing and sealing.

4.2 Procedures for cleaning application equipment and protective clothing: Rinsing with water and detergent

Effectiveness of the cleaning procedures: The product is suspensible in water. It can be removed from surfaces with water. The addition of detergent enhances the cleaning process.

4.3.1 Pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces

Pre-harvest interval (in days) for each relevant crop	Barley:	latest application at the beginning of flowering (GS 61)
	Wheat:	latest application at the end of flowering (GS 69)

Re-entry period (in days) for livestock, to areas to be grazed: Not relevant, no grazing

Re-entry period (in hours or days) for man to crops, buildings or spaces treated

XXXX has only a very limited tendency to volatilize under practical use conditions. Estimates of the fate in the troposphere resulted in half lives < 6 hours. Under practical conditions of use there is no reason for workers to enter a cereal crop shortly after treatment. Therefore a specific re-entry period is not required.

Withholding period (in days) for animal feedingstuffs:	Not relevant, no use as a feedingstuff before harvest
Waiting period (in days) between application and handling treated products:	Not relevant, crop is not handled before harvest
Waiting period (in days) between last application and sowing or planting succeeding crops:	Not relevant, no phytotoxicity and no residue exposure for succeeding crops

4.3.2 Information on any specific agricultural, plant health or environmental conditions under which the preparation may or may not be used

None of the test results obtained or observations made were such that restrictions should be imposed.

4.4 Statement of the risks arising and the recommended methods, precautions and handling procedures to minimize those risks, relating to

Handling and storage

Information on safe handling:	When using open containers, use local exhaust ventilation to prevent vapours from spreading. Make provision for product and fire-fighting water to be retained.
Information on storage:	To maintain quality, store in a dry place. Store so that unauthorised persons do not have access. Keep away from food, drink and animal feeding stuffs.

Transport information

GGVSee/IMDG Code: 1.1	UN No.: 1111	MFAG: 111 EmS: 1 11
PG: III	MPO: NO	
GGVE/GGVS: Class 3 No.	11C	RID/ADR: Class 1 No. 11C
Warning sign: Hazard no.	030	Substance no. 1111
ADNR: Class 3	No. 1 Cat 1	ICAO/IATA-DGR: 1 1111 III
Declaration for land shipment:	1.1% XXX 1111 / SOLVENT-SUSPENSION	

Declaration for sea shipment: 1.1% XXX 1111 / SOLVENT-SUSPENSION

Declaration for shipment by air: ICAO/IATA - labels: 4.1 (flammable solids) UN-Nr.:xxxx

Other information: Flammable, flash point + 00 °C. Irritating to skin and eyes. Avoid heat above + 00 °C. Keep separated from foodstuffs.

Well ventilated areas: full face mask with combination filter, *e.g.* ABEK-P2 (offers no protection from carbon monoxide!)

Enclosed premises: respirator with independent air supply. Contain fire fighting water.

Protective clothing and equipment proposed

If product is handled while not enclosed, and if skin contact may occur:

Respiratory protection: full mask with filter ABEK-P2
Hand protection: protective gloves for chemicals
Keep work area clean.
Avoid contact with product.
Keep working clothes separate from other clothing.
Change badly soiled or soaked clothing.
Wash hands before breaks and at end of work.

Fire-fighting measures:

Extinguishing media: sprayed water jet, foam, extinguishing powder, CO_2, sand.

Fight fire in early stages if safe to do so. Wear respiratory protection.

Procedures to minimize the generation of waste:

Only purchase and store quantities of product required in the short term. Do not open larger containers than is necessary for immediate requirements. Do not a mix a volume of spray solution greater than is required for immediate use.

Information on combustion products likely to be generated in the event of fire:

In the event of fire, the formation of hydrogen cyanide, carbon monoxide and nitrogen oxides must be anticipated.

4.5 Detailed procedures for use in the event of an accident during transport, storage or use

Prevent entry into drains, waters or soil. Use adsorbent material to collect spillage (*e.g.* sawdust, peat, chemical binder). Place contaminated adsorbent in closable containers. Use a damp cloth to clean floors and other objects after removal of contaminated adsorbent. Also place used cleaning materials into closable receptacles.

Protection of emergency workers and bystanders: Use the personal protective equipment proposed above.

First aid measures:

General information: Remove victims from the danger zone. Remove soiled or soaked clothing immediately.

Upon inhalation: Bring accident victims out into the fresh air. Call doctor immediately.

Following skin contact: Wash skin immediately with copious amounts of water and soap. Then seek medical advice.

Following eye contact: Rinse eyes thoroughly with water. Consult an eye specialist.

Upon swallowing: Call emergency doctor immediately.

4.6.1 Neutralization procedures (*e.g.* reaction with alkali to form less toxic compounds) for use in the event of accidental spillages

A neutralization procedure cannot be proposed (see Annex II, 3.9).

4.6.2 Pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis

Not applicable, as the product does not contain halogens.

Detailed instructions for safe disposal of the plant protection product and its packaging

Package product wastes. Close and label waste receptacles and, likewise, any uncleaned empty containers. Dispose of them at a suitable waste incineration plant in accordance with the official regulations. Where large quantities are concerned, consult the supplier.

Waste code number: 11111 old stock and remainders of crop protection and pest control products.

11111 production waste from crop protection and pest control products.

4.6.3 Methods other than controlled incineration for disposal of the plant protection product, contaminated packaging and contaminated materials

No other methods are currently available

Appendix 8	Format for the Compilation of *Tier II* Summaries - Annex III	Part 1	Section 1

Company name	Month and year	Active Substance (Name)	page of

12.3

PART 2

Section 3 Toxicological Studies (Annex III, Point 7)

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

7.2 Data on exposure

7.2.1 Operator exposure

7.2.1.1 Estimation of operator exposure

7.2.1.1.1 Estimation of operator exposure using the German model

XXXX 400 SC is applied using tractor mounted field crop sprayers with hydraulic boom and nozzles. Only applications to field crops are intended. Operator exposure estimates were calculated using the following model:

> *Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992 ("German model")*

Data used for the calculation

The following assumptions have been made in calculating operator exposure:

the area treated in one day is:	20 ha/day for field crops / tractor mounted
the application rate is:	750 g as/ha for field crops

The estimation of operator exposure was completed for two situations with regard to personal protective equipment (PPE):

no PPE: disregarding the recommendations on the label, no personal protective equipment used when handling the undiluted product and during application

with PPE: the following personal protective equipment used

- when handling the undiluted product: gloves, standard protective garment (plant protection) and sturdy footwear
- when handling the diluted product: standard protective garment (plant protection) and sturdy footwear.

It should be noted that this selection of protective measures is not intended to be a recommendation for the PPE necessary PPE when handling XXXX 400 SC. It does not take into account specific requirements which may arise in individual Member States or the necessity to wear tight-fitting goggles because of irritant effects for eyes. Additional PPE can be used to further reduce the exposure of the operator.

Calculation for field crops / tractor mounted

Amount handled per day = treated area x use rate = 20 ha/day x 0.75 kg as/ha = 15.0 kg as/day

No PPE

I_m	= 0.0006	mg/kg as x 15.0 kg as/day	=	0.009	mg/person and day
D_m	= 2.4	mg/kg as x 15.0 kg as/day	=	36.0	mg/person and day
I_a	= 0.001	mg/kg as x 15.0 kg as/day	=	0.015	mg/person and day
$D_{a(c)}$	= 0.06	mg/kg as x 15.0 kg as/day	=	0.90	mg/person and day
$D_{a(h)}$	= 0.38	mg/kg as x 15.0 kg as/day	=	5.70	mg/person and day
$D_{a(b)}$	= 1.6	mg/kg as x 15.0 kg as/day	=	24.0	mg/person and day

With PPE

I_m	= 0.0006	mg/kg as x 15.0 kg as/day	=	0.009	mg/person and day
D_m	= 2.4	mg/kg as x 15.0 kg as/day x 0.01*	=	0.36	mg/person and day
I_a	= 0.001	mg/kg as x 15.0 kg as/day	=	0.015	mg/person and day
$D_{a(c)}$	= 0.06	mg/kg as x 15.0 kg as/day	=	0.90	mg/person and day
$D_{a(h)}$	= 0.38	mg/kg as x 15.0 kg as/day	=	5.70	mg/person and day
$D_{a(b)}$	= 1.6	mg/kg as x 15.0 kg as/day x 0.05*	=	1.20	mg/person and day

Abbreviations: I = estimated inhalation exposure; m = during mixing/loading; a = during application
D = estimated dermal exposure (c) = head; (h) = hands;
(b) body * reduction coefficient

A summary of the expected operator exposures is provided in the following tables

Table 7.2.1.1.1-1: Estimated operator exposure / no PPE

Dermal exposure	[mg/person/day]
Mixing/loading	36.0
Application	30.6
Total	66.6
Inhalation exposure	
Mixing/loading	0.009
Application	0.015
Total	0.024

Table 7.2.1.1.1-2: Estimated operator exposure / with PPE

Dermal exposure	[mg/person/day]
Mixing/loading	0.36
Application	7.80
Total	8.16
Inhalation exposure	
Mixing/loading	0.009
Application	0.015
Total	0.024

Determination of the tolerable exposure (see also 5.10.2.2 of Annex II, *Tier II*)

The following NOELs were obtained in toxicological studies relevant to operator safety with XXXX:

Study type	NOEL
subacute dermal rabbit	5 mg/kg bw/day (systemic NOEL)
subacute inhalation rat	14.3 mg/m^3 air (corresponding to 5.1 mg/kg bw/day)

In the subacute dermal study, 5 mg/kg bw/day was the highest dose tested, because of animal welfare considerations - the irritant action of XXXX. It can be assumed from the results of the subacute and subchronic oral toxicity studies that the actual systemic NOEL after dermal application is substantially higher than 5 mg/kg bw/day.

Using a safety factor of 25 the tolerable dermal (D_{tol}) and inhalation exposure (I_{tol}) are calculated to be:

D_{tol} = 5 mg/kg bw x 70 : 25 = 14 mg/person/day

I_{tol} = 5.1 x 70 : 25 = 14.28 mg/person/day

Comparison of estimated and tolerable exposure

Using the following equation, the total degree of exposure (E) can be calculated for the two conditions of operator protection assumed; values of E < 1 indicate that no risk for the applicator exists.

$$E = \frac{I}{Itol} + \frac{D}{Dtol}$$

a) no PPE

$$E = \frac{0.024}{14.28} + \frac{66.6}{14} = \quad 0.0017 + 4.757 = \mathbf{4.76}$$

b) with PPE

$$E = \frac{0.024}{14.28} + \frac{8.16}{14} = \quad 0.0017 + 0.583 = \mathbf{0.58}$$

Assessment

The results of the calculations using the German model show, that inhalation exposure is not critical. When assessing the risk of dermal exposure to XXXX, it must be taken into account that the highest dose tested in the subacute dermal study was determined in the light of the irritation potential for rabbits. The actual systemic NOEL is assumed to be substantially higher. Nevertheless, when applying the model with the available NOEL, a sufficient margin of safety exists for XXXX with regard to systemic toxicity if standard protective equipment is used.

7.2.1.1.2 Estimation of operator exposure using the UK model

XXXX 400 SC is applied using tractor mounted field crop sprayers with hydraulic boom and nozzles. Only applications to field crops are intended. Operator exposure estimates were done using the "UK model" (Predictive Operator Exposure Model (POEM), UK MAFF, 1992).

Data used for the calculation	Area treated per day:	50 ha
	Application dose:	750 g as/ha
	Container:	5 litres with 51 mm opening

Penetration of gloves

Results of tests to measure the penetration of XXXX 400 SC through gloves have shown that only extremely low amounts penetrate (Maasfeld, 1995). Therefore, no relevant exposure of the operator's hands is expected when gloves are worn. The 5 % penetration value used for the calculation (mixing/loading and application) must be regarded to be a worst case assumption which overestimates exposure.

Absorption data

The absorbed dose, following inhalation exposure, was calculated on the basis of the assumption that there is 100 % retention and absorption of inhaled material.

The dermal absorption of XXXX from the product (XXXX 400 SC) was investigated under *in vivo* conditions in the rat and *in vitro* using rat and human skin. Tests were done with the undiluted product and a 1:100 dilution, which slightly exceeds the maximum field use concentration (1.5 : 200).

A summary of the dermal absorption data on XXXX 400 SC is provided at point 7.3.

The calculations that follow were done using a 5 % skin absorption figure for both mixing/loading and application.

Personal protective equipment

The calculation of the estimated operator exposure was made for different scenarios with respect to personal protective equipment (PPE):

no PPE:	disregarding the recommendations on the label, no personal protective equipment used, when handling the undiluted product and during application
with PPE:	gloves, standard protective garment (plant protection) and sturdy footwear, worn when handling the diluted and the undiluted product
gloves:	during mixing/loading and during application.

Poem calculations

The calculations were performed using the relevant spreadsheet. Results obtained are given in the following table.

Table 7.2.1.1.2-1: POEM calculation for tractor mounted field crop application

A	PRODUCT DATA			
1	Product name	XXXX 400 SC		
2a	Active ingredient	XXXX		
2b	Concentration	500	mg/ml	
3	Formulation type	EC		
4a	Main solvent			
4b	Concentration of solvent	na		
5	Maximum in-use as concentration	3.750	mg/ml	
B	EXPOSURE DURING MIXING AND LOADING			
1a	Container size	5	litres	
1b	Hand contamination/operation	0.01	ml	
2	Application dose	1.5	litres product/ha	37.5 kg as/day
3	Work rate	50	ha/day	
4	Number of operations	15	/day	
5	Hand contamination	0.15	ml/day	
6	**Protective clothing**	**None**		**Gloves**
7	Transmission to skin	100		5 %
8	Dermal exposure to formulation	0.15		0.0075 ml/day
9	Concentration of as	500		500 mg/ml
10	Dermal exposure to as	75,000		3,750 mg/day
11	Percent absorbed	5		5 %
12	**Absorbed dose**	**0.063**		**0.003** mg/kg bw/day

C EXPOSURE DURING SPRAY APPLICATION

1	Application technique	- Vehicle with cab boom hydraulic nozzles				
2	Application volume	200	spray/ha			
3	Volume of surface contamination	10	ml/h			
4	Distribution	Hands	Hands	Trunk	Legs	
		65	65	10	25	%
5	Clothing	NONE	GLOVES	PERMEABLE	PERMEABLE	
6	Penetration	100	5	5	15	%
7	Dermal exposure	6.5	0.325	0.05	0.375	ml/h
8	Duration of exposure	6	h			

	PPE	NONE	GLOVES	
9	Total dermal exposure to spray	41.55	4.5	ml/day
10	Concentration of as	3.750	3.750	mg/ml
3	Dermal exposure to as	155.813	16.875	mg/day
11	Percent absorbed	5	5	%
12	**Absorbed dose**	**0.130**	**0.014**	**mg/kg bw/day**

E INHALED EXPOSURE DURING SPRAY APPLICATION

1	Inhalation exposure	0.01	ml/h
2	Duration of exposure	6	h
3	Concentration of as	3.750	mg/ml
4	Inhalation exposure to as	0.225	mg/day
5	Percent absorbed	100	%
6	**Absorbed dose**	**0.004**	**mg/kg bw/day**

F PREDICTED EXPOSURE

1	No gloves	0.196	mg/kg bw/day
2	Gloves only when mixing/loading	0.137	mg/kg bw/day
3	Gloves only during spray application	0.077	mg/kg bw/day
4	Gloves during spray application & mixing/loading	0.021	mg/kg bw/day

Determination of tolerable exposure

For XXXX an acceptable operator exposure level (AOEL) of 0.4 mg/kg bw/day has been proposed (see Annex II point 5.10.2.2). For a 60 kg person this corresponds to 24 mg active substance per day. The AOEL is based on the systemic NOEL established in subacute/subchronic toxicological studies (10 mg/kg bw/day). In the context of the quality, extent and consistency of the toxicological data base available and the results of the absorption, distribution, and excretion studies reported, a safety factor of 25 is considered to be appropriate for XXXX.

Assessment

The portion of the AOEL which is accounted for by the estimated exposure, was calculated to be as follows:-

Table 7.2.1.1.2-2: Portion of AOEL claimed by the expected operator exposures

	% of AOEL claimed
no PPE	49.00 %
gloves only when mixing/loading	34.25 %
gloves only during spray application	19.25 %
gloves during mix/loading and spray application	5.25 %

The results of the POEM calculations show that only 50 % of the AOEL is accounted for under practical conditions of use, where no personal protective equipment is used. Therefore harmful effects from exposure to XXXX do not arise for operators wearing the recommended personal protective equipment. However, because of the skin irritant properties of XXXX 400 SC it is absolutely necessary to wear gloves during mixing/loading. Where gloves are worn during mixing/loading, the estimated exposure is no more than 34 % of the proposed AOEL.

It can be concluded that XXXX 400 SC can be handled safely under the recommended conditions of use.

7.2.1.2 Measurement of operator exposure

Since the risk assessment carried out indicated that the health-based limit value (AOEL) will not be exceeded under practical conditions of use, a study to provide a measure of operator exposure to XXXX 400 SC under field conditions, was not necessary and therefore was not carried.

7.2.2 Bystander exposure

Given the low vapour pressure of XXXX 400 SC and its low inhalation toxicity, problems for bystanders by the inhalation route are not anticipated. Dermal exposure due to drift of spray material, calculated using spray drift rates established under practical conditions of use, indicated that the worst case exposure (person standing at the edge of the area being treated during a full working day) was likely to be less than 00 % of the AOEL.

7.2.3 Worker exposure

XXXX 400 SC is normally used at times, when it is not necessary to enter crops shortly after spraying. It is therefore not necessary to determine a particular re-entry time for workers. In cases where re-entry is not avoidable, personal protective equipment similar to those of the operator (gloves and standard protective garment) is regarded to provide sufficient protection.

7.3 Dermal absorption

The dermal absorption of XXXX from the product (XXXX 400 SC) was investigated under *in vivo* conditions in the rat and *in vitro* using excised rat and human skin. Tests were done with the undiluted formulation and with a 1:100 dilution, a dilution rate which slightly exceeds the maximum field use concentration (1.5 : 200).

The results are summarised in the following table.

Table 7.3-1: ***Dermal absorption of XXXX in different test systems; results are expressed as % active ingredient absorbed during 8 and 24 h.***

		neat product	*1:100*	*Reference*
in vivo - rat	8 hr	13.1 %	62.4 %	Weber, 1994
	24 hr	23.6 %	60.7 %	
in vitro - rat skin	8 hr	0.26 %	5.18 %	Brain *et al*, 1994
	24 h	1.69 %	26.84 %	
in vitro - human skin	8 hr	0.02 %	0.30 %	Brain *et al*, 1994
	24 hr	0.35 %	1.84 %	

From these data, dermal absorption figures for "human skin *in vivo*" can be calculated, using the following formula:-

$$\textit{in vivo}\ \text{human} = \frac{\textit{in vitro}\ \text{human} \times \textit{in vivo}\ \text{rat}}{\textit{in vitro}\ \text{rat}}$$

The calculated results obtained are given in the next table:-

Table 7.3-2: Dermal absorption of XXXX extrapolated for human skin in vivo

	neat product	*1 : 100*
8 h	1.0 %	3.6 %
24 h	4.9 %	4.2 %

It is to be noted that the operator exposure calculations referred to at point 7.2.1, were done using a 5 % dermal absorption figure for mixing/loading and application.

7.4

PART 3

Section 6 Ecotoxicological Studies (Annex III, Point 10)

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation has been amended to protect the commercial interests of the owner of the data.

Applicant should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Competent Authority of the Member State to which application is to be made.

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10.1 *Effects on Birds*

Birds and mammals may be exposed to XXXXXX mainly by the consumption of contaminated feed. The expected typical maximum residue levels on leaves, insects and seeds were calculated according to Hoerger and Kenaga (1972). Information relating to crops, application rates and intervals is given in Table 10.1-1. The values of the expected initial residue concentrations of XXXXXX and for the highest possible level of daily intake by birds and mammals are provided in Table 10.1-2 and 10.1-3.

To calculate the highest possible level of daily intake of XXXXXX by birds and mammals, it was assumed that small birds (*ca* 20 g bw) consume approximately 30 % of their body weight per day, whereas bigger animals (>100 g bw) ingest approximately 10 % of their body weight daily.

Long term predicted environmental concentrations (PEC_{lt}), were calculated as the time weighted average concentration for the respective time interval according to the formula

$$PEC_l = PEC_i \cdot \frac{DT50}{t_l \cdot \ln(2)} (1 - e^{(-t_l \cdot \ln(2)/DT50)})$$

where PEC_{lt} = time weighted average concentration, PEC_i = initial concentration, DT50 = half-life for dissipation and t_l = time period concerned.

For these calculations, the mean of the measured half-life in plant material of XXXXXX in different crops of 7.6 days was used (average from 21 studies, RA-reports: XXX, YYY, ZZZ ....; see Annex II, point 6). For the purposes of the calculation, the application rates and intervals given in Table 10.1-1 were used. That application scenario was chosen in order to approach a realistic worst-case situation relevant to commercial practice.

The estimated time weighted average concentration in green mass was arrived at by extrapolation from the *normalized* area under the curve for the actual estimated concentration values. This concept is depicted in Figures 10.1-1 and 10.1-2, while the values are given in Tables 10.1-4 and 10.1-5.

Table 10.1-1: Crops, application rates and intervals

Crop	Application (maximum frequency)	mean or highest rate assigned g as/ha
grapes	3 applications/10d interval	500
tomatoes	3 applications/10d interval	750
fruit trees	4 applications/10d interval	750
berries	4 applications/10d interval	1000

Table 10.1-2 Exposure of birds and mammals

Target culture / crop	Application rate kg as/ha	typical maximum initial residue concentration (mg as/kg feed) according to Hoerger & Kenaga, 1972			
		leaves	small insects	diet of small + bigger insects	seeds or bigger insects
grapes	0.5	15.63	14.73	8.04	1.34
tomatoes	0.75	23.44	22.10	12.05	2.01
fruit trees	0.75	23.44	22.10	12.05	2.01
berries	1.0	31.25	29.46	16.07	2.68

Table 10.1-3: Exposure of birds and mammals

Target culture / crop	Application rate kg as/ha	Maximum daily intake of as (mg/kg bw/day): leaves / small insects / diet of small and bigger insects / seeds or bigger insects							
		small animals (*ca* 20 g bw) *				bigger animals (> 100 g bw) **			
grapes	0.5	4.69	4.42	2.41	0.40	1.56	1.47	0.80	0.13
tomatoes	0.75	7.03	6.63	3.62	0.60	2.34	2.21	1.21	0.20
fruit trees	0.75	7.03	6.63	3.62	0.60	2.34	2.21	1.21	0.20
berries	1.0	9.38	8.84	4.82	0.80	3.13	2.95	1.61	0.27

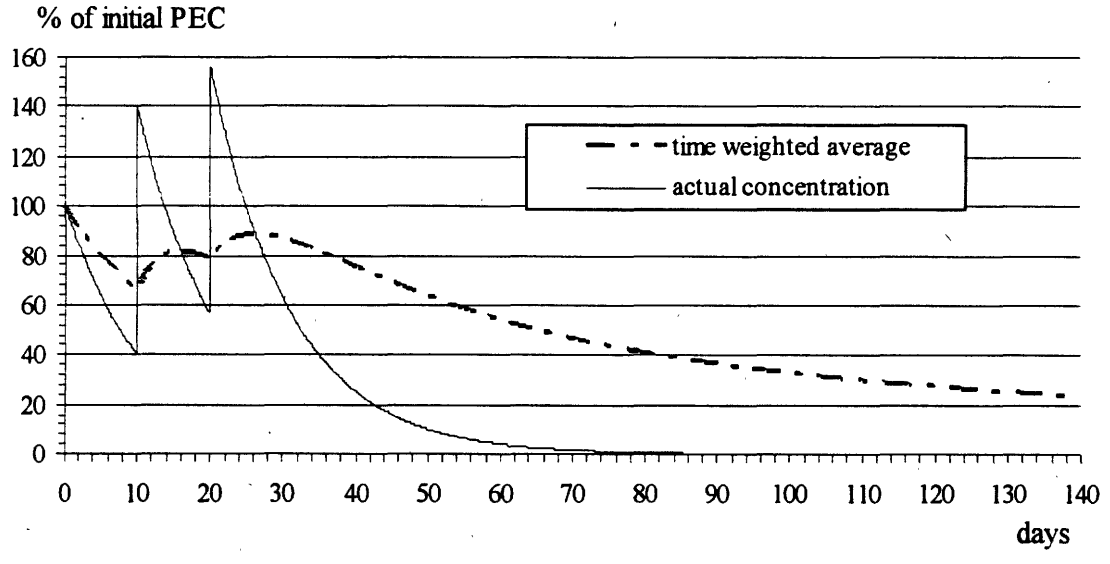
* for small animals (*ca.* 20 g bw) daily feed consumption of 30 % of body weight is assumed,
** for bigger animals (> 100 g bw) daily feed consumption of 10 % of body weight is assumed

Spray schedule based on 3 applications with an interval of 10 days in between as used in grapes and tomatoes:-

Table 10.1-4: Time course of the PEC of XXXXXX in plant material (example: half life 7.6 days)

(d)	actual concentration (% of initial)	time weighted average (% of initial)
0	100.00	100.00
1	91.28	95.21
2	83.33	91.06
4	69.43	83.47
5	63.38	80.00
7	52.81	73.63
14	97.32	80.70
21	142.68	82.62
28	75.35	88.23
42	21.02	72.95
60	4.07	54.15
90	0.26	36.56
91	0.24	36.16
147	0.00	22.40
161	0.00	20.46
360	0.00	9.15

Figure 10.1-1: Time course of the PEC of XXXXXX in plant material (example: half life 7.6 days)

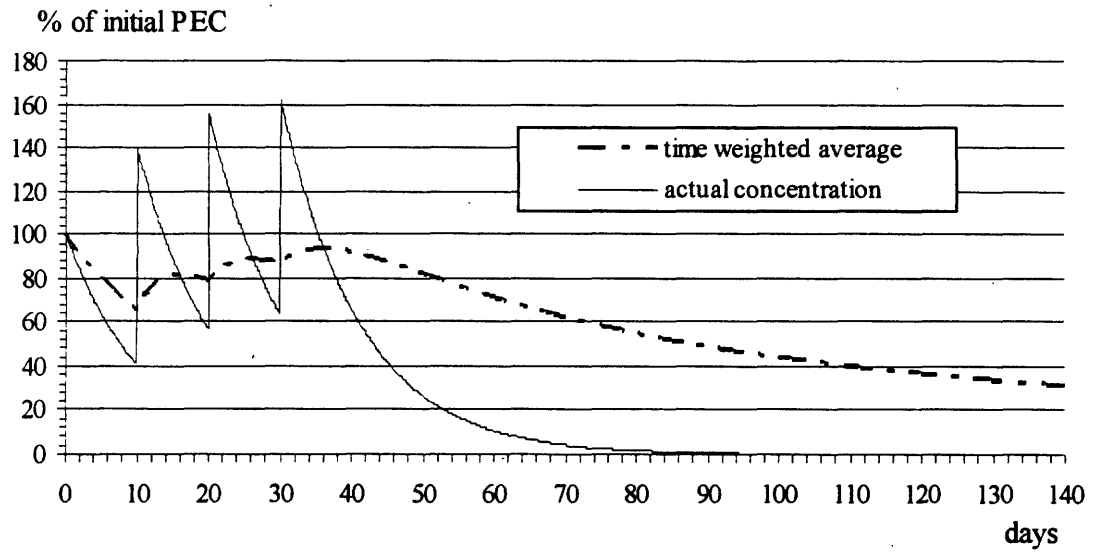


Spray schedule based on 4 applications with an interval of 10 days in between as used in fruit trees and berries:-

Table 10.1-5: Time course of the PEC of XXXXXX in plant material (example: half life 7.6 days)

(d)	actual concentration (% of initial)	time weighted average (% of initial)
0	100.00	100.00
1	91.28	95.21
2	83.33	91.06
4	69.43	83.47
5	63.38	80.00
7	52.81	73.63
14	97.32	80.70
21	142.68	82.62
28	75.35	88.23
42	54.49	90.45
60	10.55	71.31
90	0.68	48.74
91	0.62	48.21
147	0.00	29.89
161	0.00	27.29
360	0.00	12.21

Figure 10.1b: Time course of the PEC of XXXXXX in plant material (example: half life 7.6 days)



10.1.1 Acute oral toxicity

Report: Grau, R. (1995): XXXXXX technical - acute oral toxicity to bobwhite quail. Bayer AG, unpublished report No: YYYY [14]

Guidelines: EPA § 71-1
Deviations: Only two dose levels

GLP: yes

Material and methods: XXXXXX, purity: 95.7%, Specification (see Annex II, point 1), single oral administration in gelatine capsules without any carrier to adult Bobwhite Quail (26-week-old): 1050 or 2000 mg as/kg bw; subsequent observation period of 14 days.

Findings:

Acute oral toxicity to birds

Test substance	TG as
Test object	Bobwhite quail ♂& ♀
LD_{50} mg as/kg bw	> 2000
Lowest observed effect level (LOEL) mg as/kg bw	2000
Highest tested dose without toxic effect (NOEL) mg as/kg bw	1050
Toxic threshold effect level, TEL (mean LOEL-NOEL) mg as/kg bw	1449

Observations: The LD_{50} value, the lowest observed effect level (LOEL), and the no effect dose (NOEL) are listed in the Table. The LD_{50} value was determined to be greater than 2000 mg as/kg bw.

Single oral doses of 1050 and 2000 mg as/kg bw were given. No mortalities were observed. The no observed effect level (NOEL) was 1050 mg as/kg bw based on dose dependent statistically significant differences in body weight development over the full observation period in female birds. On the basis of visible symptoms, the NOEL was ≥ 2000 mg as/kg bw.

Gross pathology: No visible effects on body organs were visible at post-mortem examination of birds from the 2000 mg as/kg bw treatment level.

Conclusion: XXXXX has no acute oral toxicity to birds. In view of these findings, further studies using the formulated product were not conducted

Risk assessment: The highest potential levels of intake of XXXXXX by small birds are associated with residues on seeds or insects (1:1 ratio, small and bigger insects). At application rates between 0.5 and 1.0 kg as/ha the highest likely daily XXXXXX intake by small birds was calculated as 4.82 to 0.4 mg as/kg bw/day (Table 10.1-3). Accordingly, the minimum acute toxicity/exposure ratio ($TER_a = LD_{50}/ETE_i$) for small birds is > 415 (insects) to > 4978 (seeds).

Larger birds with a body weight of greater than 100 g, that feed partly on leaves (diet of 10 % leaves and 90 % insects) may be exposed to higher residue levels but their *body weight/daily feed intake* ratio is lower (assumed

[14] The description of this test, which relates to the toxicity of the active substance, is repeated here for the convenience of the reader

to be 0.1, or 10%). In this case, the TER_a for application rates between 0.5 and 1.0 kg as/ha is >1137 to >14933 based on intake figures for XXXXXX of 1.76 to 0.13 mg as/kg bw/day (Table 10.1-3).

The time weighted average concentration for a time period of 5 days is expected to be 80 % of initial concentration (*cf* Table 10.1-4 and 10.1-5). On the basis of diets of 90 % insects and 10 % leaves or of seeds, the short term TER_{st} (LC_{50}/PEC_{5d}) for birds is calculated to be > 355 and > 4667, respectively [see Annex II, chapter 8.1.2; 5-day dietary for Bobwhite quail and mallard duck LC50 > 5000 mg as/kg feed].

The time weighted average concentration (*cf* Table 10.1-4 and 10.1-5) for a time period of 23 weeks would be 20.46 or 27.29 % of an initial concentration, based on 3 or 4 repeated applications for the different crops concerned. Based on diets of 90 % insects and 10 % leaves or of seeds, the long term TER_{lt} ($NOEC/PEC_{161d}$) for birds is calculated to be between 432 and 7569 [see Annex II, chapter 8.1.3; 23-week reproduction Bobwhite quail NOEC = 2074 mg as/kg feed].

Furthermore, it is very unlikely that birds under field conditions would consume exclusively contaminated feed. Therefore a risk to birds arising from dietary exposure can be excluded.

10.1.2 Supervised cage or field trials

Due to the high acute, short term and long term toxicity/exposure ratios (TER_a, TER_{st}, TER_{lt}) for the active substance, no further studies are considered necessary. Risks to birds from residues of XXXXXX can be excluded.

10.1.3 Acceptance of bait, granules, or treated seeds by birds

Not applicable for plant protection products intended for application by spraying.

10.1.4 Effects of secondary poisoning

Use of plant protection products containing active substances having a high bioaccumulation potential could theoretically result in risks for birds as a result of secondary poisoning. The steady state bioconcentration factor for XXXXXX in a laboratory study with bluegill sunfish (whole fish), was determined to be in the range of 132-185 (mean 159, see Annex II, paragraph 8.2.3). The initial aquatic PEC, based on 1m and 30 cm water depth and different drift rates of 0.6-1.5 %, is in the range of 0.45 to 3.75 µg as/L (*cf* Table 10.2-1). Theoretically, maximum concentrations in fish could, for a short time, reach a level of about 0.072 - 0.596 mg as/kg (PEC - values multiplied by the mean BCF of 159). Based on the acute toxicity for birds of XXXXXX (LD_{50} of > 2000 mg as/kg bw - *cf* paragraph 10.1.1), the maximum concentration in fish of 0.072-0.596 mg as/kg and the assumption of a daily feed intake of 10 % of the body weight, the TER_a was calculated to be > 279525 to > 33543. For short term exposure, a TER_{st} of > 69881 to > 8386 was calculated, based on the LC_{50} for birds of >5000 mg as/kg feed (see Annex II, paragraph 8.1.2) and on XXXXXX concentrations of 0.072-0.596 mg as/kg fish.

In conclusion, a risk to birds as a consequence of the bioaccumulation of XXXXXX does not arise.

10.2 Effects on aquatic organisms

Aquatic organisms may be exposed to plant protection products as a result of emissions from treated fields. The studies and date provided permit a risk assessment to be generated relevant to exposure to XXXXXX under practical conditions of use of plant protection products containing the compound.

PEC_{sw} in standing water bodies [15]

The initial maximum PEC value (PEC_i) was calculated on the basis of spray drift rates established for different crops by the German BBA/UBA (Ganzelmeier *et a*, 1995), for water depths of 0.3 and 1.0 m in a standing water body.

Relevant information with respect to crops, application rates and intervals is provided in Table 10.1-1. Assuming first order kinetics for decline in concentrations, longer term predicted environmental concentrations (PEC_l) were calculated as the time weighted average concentration for the respective time interval from first application onwards (*cf* Table 10.2-1).

If in such a scenario, the drift assumptions developed by the German BBA/UBA are used (95 percentile of single point values in a water body), the probability of reaching (or exceeding) the predicted concentrations after all applications will drop from 0.05 (5 % or once in 20 years) after 1 application to 0.0025 (0.25 % or once in 400 years) after 2 applications and to 0.000125 (0.0125 %) after 3 applications.

The time weighted average (TWA) was calculated according to the formula

$$PEC_l = PEC_i \cdot \frac{DT50}{t_l \cdot \ln(2)} \left(1 - e^{(-t_l \cdot \ln(2)/DT50)}\right)$$

where PEC_l = time weighted average concentration, PEC_i = initial concentration, DT50 = half-life of dissipation and t_l = considered time period.

For these calculations, the half-life measured in the supernatant water of the two water sediment studies reported (mean: 2.1 d = 50.4 h) was used (Brumhard, 1997).

The estimated time weighted average concentration in water was arrived at by extrapolation from the *normalized* area under the curve for the actual estimated concentration values. This concept is depicted in Figures 10.2-1 and 10.2-2, while the values given in Tables 10.2-2 and 10.2-3.

[15] The PEC calculations provided in this Annex III *Tier II* summary, at point 9.2, are repeated here for the convenience of the reader

Table 10.2-1: Exposure of aquatic organisms – ground application # (standing water = worst case)

Crop	Distance (m)	Drift (%)	Application rate (as)		Portion of drift (as)		initial PECsw (µg as/L) related to a water depth of	
			kg/ha	mg/m²	kg/ha	mg/m²	1 m	30 cm
grapes *	10	1.5	0.500	50.0	0.008	0.750	0.75	2.50
tomatoes	5	0.6	0.750	75.0	0.005	0.450	0.45	1.50
fruit trees *	20	1.5	0.750	75.0	0.011	1.125	1.13	3.75
berries °	15	0.8	1.000	100.0	0.008	0.800	0.80	2.67

Ganzelmeier *et al*, 1995 * late growth stages ° more than 50 cm high

PEC_{sw} in slow moving water bodies [15]

The initial concentration calculated for the purposes of risk assessment with respect to stagnant waters was based on measured drift rates (Ganzelmeier *et al*, 1995). The data are generally above the 95-percentile of downwind measured values and therefore represent a worst-case situation, which can only be expected in exceptional cases. For the purposes of calculation it was also assumed that drift reaches standing shallow waters or the benches of larger surface waters without water exchange or circulation.

For the calculation of long-term exposure the time weighted average concentration, taking into account degradation in aqueous systems, is provided. This time weighted average concentration depends not only on the initial concentration but also on the half-life value of the substance in the water column of a water-sediment-system. It must be emphasized that the use of 2 or 3 times the highest concentration (95 percentile) in a spray sequence is an unrealistic worst case (probability about zero). This scenario is exceptionally used pending the availability of more realistic calculation methods which are under development.

In principle the same assumptions are valid for moving waters. Following similar levels of contamination the half-life in moving waters is necessarily lower than in standing waters, as in addition to degradation and adsorption (*e.g.* into the sediment) dilution occurs (inflow). In addition, exposure at the location observed is quickly diminished, since the contaminated water is carried forward (outflow). Therefore both the extent and duration of exposure are reduced, the faster the waters are moving.

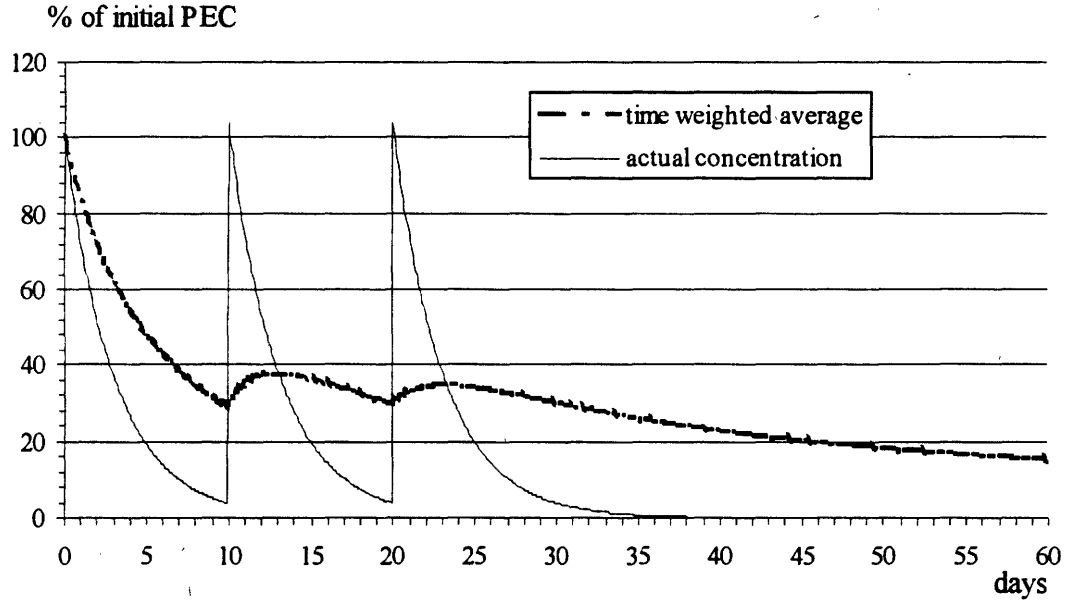
Consequently exposure in stagnant waters is regarded as the worst case. Corresponding exposure calculations for moving waters always provide a more favourable result at equal levels of contamination. If exposure, as calculated for standing waters, does not result in any unacceptable effects, no unacceptable effects can be assumed in the case of moving waters. Therefore the calculation of exposure in moving waters is deemed to be unimportant for the purposes of risk assessment.

Spray schedule based on 3 applications with an interval of 10 days in between as used in grapes and tomatoes (+ remark on probability, point 10.2):-

Table 10.2-2: Time course of the PEC of XXXXXX in water (example: half life 2.1 days)

(d)	actual concentration (% of initial)	time weighted average (% of initial)
0	100.00	100.00
1	71.89	84.01
2	51.68	72.20
4	26.71	54.75
5	19.20	48.29
7	9.92	38.45
14	27.69	37.37
21	74.63	32.86
28	7.40	31.82
42	0.07	21.74
58	0.00	15.74
96	0.00	9.51
147	0.00	6.21

Figure 10.2-1: Time course of the PEC of XXXXXX in water (example: half life 2.1 days)

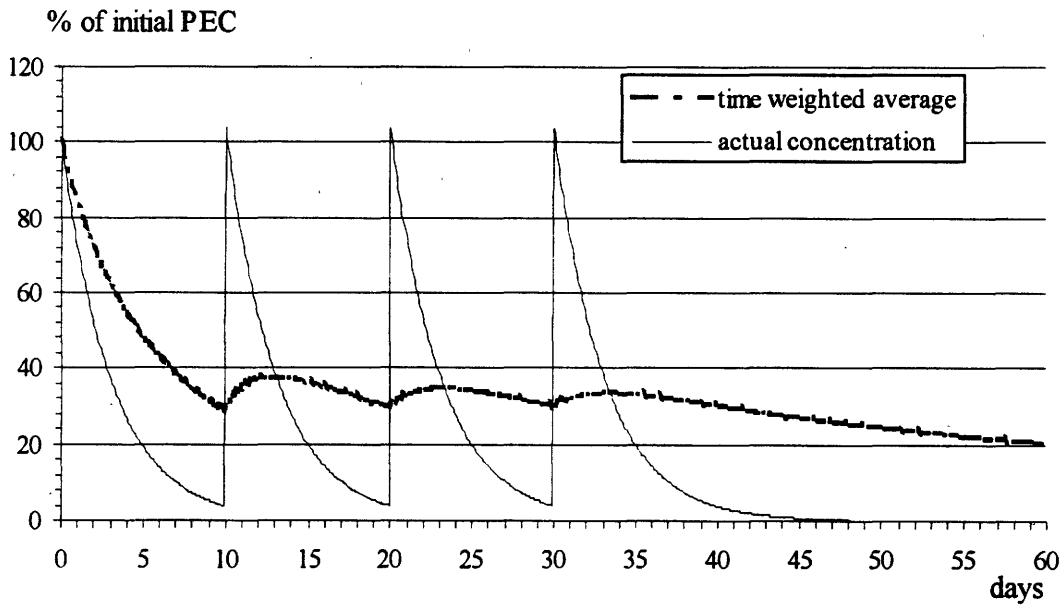


Spray schedule based on 4 applications with an interval of 10 days in between as used in fruit trees and berries. (see remark on probability, point 10.2):-

Table 10.2-3: Time course of the PEC of XXXXXX in water (example: half life 2.1 days)

(d)	actual concentration (% of initial)	time weighted average (% of initial)
0	100.00	100.00
1	71.89	84.01
2	51.68	72.20
4	26.71	54.75
5	19.20	48.29
7	9.92	38.45
14	27.69	37.37
21	74.63	32.86
28	7.40	31.82
42	1.98	28.91
58	0.01	21.04
96	0.00	12.71
147	0.00	8.30

Figure 10.2-2: Time course of the PEC of XXXXXX in water (example: half life 2.1 days)



10.2.1 Acute toxicity to fish, aquatic invertebrates or effects on algal growth

Acute toxicity to fish

Report: Dorgerloh, M.(1996):XXXXXX WG 50 - Acute toxicity (96 hours) to rainbow trout (*Oncorhynchus mykiss*) in a semi-static test.
Bayer AG, unpublished report No: YYYY

Guidelines: OECD 203 and EEC C.1
Deviations: none

GLP: yes (certified laboratory)

Material and methods: XXXXXX WG 50, purity: 49 %, Specification: (Batch No.: 0222 based on 04258/0214, Development No.: 170928), rainbow trout (*Oncorhynchus mykiss/* lot F3/ 96*)*: 10 fish per test concentration (mean body length 4.7 cm, mean body weight 1.2 g) for 96 h under semi-static conditions.

Findings:

Toxicity to fish

Test substance	50 WG
Test object	rainbow trout
Exposure	96h, semi-static
LC_{50} mg as/L	1.30
lowest tested conc. with effect (LOEC) mg as/L	0.92
highest tested conc. without effect (NOEC) mg as/L	0.46
Threshold effect concentration, TEC (mean LOEC-NOEC) mg as/L	0.65

Observations: The results are provided in summary form in the Table. Nominal test substance concentrations ranged from 0.94 to 15.0 mg/L. Analytical data showed mean measured levels from 91-96% of the nominal values, so nominal values were used in reporting results. The 96-hour LC_{50}, NOEC and LOEC values were 2.66, 0.94 and 1.88 mg test substance/L, equivalent to 1.30, 0.46 and 0.92 mg as/L respectively. In comparison to these results the LC_{50} and NOEC values found in a similar test on rainbow trout but using XXXXXX technical as were 1.24 and 0.94 mg as/L respectively (*cf* Annex II, paragraph 8.2.1).

Conclusion: XXXXXX 50 WG is of moderate toxicity to rainbow trout.

Risk assessment: The PEC_i varies depending on distance from and the depth of the water body. For the use pattern presented in Table 10.1-1 and the distances from water body as well as the resulting drift rates presented in Table 10.2-1, initial concentrations of between 0.45 and 3.75 µg as/L for 1 m and for 30 cm water depths were calculated (Table 10.2-1). On the basis of the acute LC_{50} value for fish (1.3 mg as/L) and the PEC_i, acute TERs between 2889 and 347 were derived.

The chronic toxicity of XXXXXX technical, to early life stages of rainbow trout was determined under flow-through test conditions with a study duration of 96 days (*cf* Annex II, paragraph 8.2.2.2). The lowest NOEC for XXXXXX technical was found to be 101 µg as/L, on the basis of the most sensitive end point (time to swim-up).

Concentrations in natural water bodies decrease over time (*cf* Figures 10.2-1 and 10.2-2). Consequently the PEC_{lt} for a specified time period (*e.g.* duration of the test) will be lower than the PEC_i (*cf* Tables 10.2-1, 10.2-2 and 10.2-3). The time weighted average concentration for the exposure period of the chronic test was calculated to be 9.51 or 12.71 % of the initial PEC, based on 3 or 4 repeated applications for the different crops. Accordingly, a long term TER ($NOEC/PEC_{96d}$) for fish of 212 to 2360 can be derived.

Acute toxicity to *Daphnia magna*

Report: Heimbach, F. (1995): Acute toxicity of XXXXXX WG 50 to waterfleas (*Daphnia magna*). Bayer AG, unpublished report No: YYYY

Guidelines: OECD 202 and EPA-FIFRA 72-2
Deviations: none

GLP: yes (certified laboratory)

Material and methods: XXXXXX WG 50, purity: 49.6 %, Specification (Batch No.: 0222 according to 4258/0214); first instars of *Daphnia magna* (< 24 h old) in a static test system were exposed for 48 h to nominal concentrations ranging from 2.02 to 202 mg formulation./L.

Findings:

Test substance	50 WG
Test object	*Daphnia magna*
Exposure	48h, static
EC_{50} mg as/L	105
lowest tested conc. with effect (LOEC) mg as/L	32
highest tested conc. without toxic effect (NOEC) mg as/L	18
Threshold effect concentration, TEC (mean LOEC-NOEC) mg as/L	24

Observations: The results are provided in summary form in the Table. Analytical data showed measured levels from 103 - 111% of nominal. Nominal values were therefore use in reporting results. The 48-hour EC_{50} value for *Daphnia magna* exposed to XXXXXX WG 50 was 211 mg/L test substance, equivalent to 105 mg as/L. The NOEC and LOEC values were 36 and 65 mg/L test substance, equivalent to 18 and 32 mg as/L.

In comparison to the EC_{50} and NOEC values found in a similar test on waterfleas using XXXXXX technical as (> 18.8 and 10.1 mg as/L respectively; Annex II, paragraph 8.2.4) there is very close agreement with the values from the 50 WG study.

Conclusion: XXXXXX WG 50 has a low acute toxicity to *Daphnia magna*.

Risk assessment: The PEC_i varies depending on distance from and the depth of the water body. For the use pattern presented in Table 10.1-1 and the distances from water body as well as the resulting drift rates presented in Table 10.2-1, initial concentrations between 0.45 and 3.75 µg as/L for 1 m and for 30 cm water depth were calculated (*cf* Table 10.2-1). On the basis of the acute EC_{50} value for *Daphnia* (105 mg as/L) and the PEC_i, acute TERs between 233333 and 28000 can be derived.

The effect of XXXXXX technical on the reproduction of water fleas was determined in a 21-days laboratory study under semistatic test conditions (*cf* Annex II, paragraph 8.2.5). The highest concentration tested which was without toxic effect (NOEC) was 1.0 mg as/L.

Concentrations in natural water bodies decrease over time (*cf* Figures 10.21 and 10.2-2). Consequently the PEC_{lt} for a specified time period (*e.g.* duration of the test) will be lower than the PEC_i (*cf* Tables 10.2-1, 10.2-2 and 10.2-3). The time weighted average concentration for the exposure period of the chronic test is calculated to be 32.86 % of the initial PEC value. Accordingly, a long term TER ($NOEC/PEC_{21d}$) for Daphnia of 812 to 6763 can be derived.

Effects on algal growth

Report: Anderson, J. P. E. (1995):Influence of XXXXXX WG 50 on the growth of the green alga, *Selenastrum capricornutum*.
Bayer AG, unpublished report No: YYYY

Guidelines: OECD 201, EEC Directive 79/831/E, ISO 8692
Deviations: None

GLP: yes (certified laboratory)

Material and methods: XXXXXX WG 50, purity: 49.6 %, Specification (Batch No.: 0222 after 4258/0214); *Selenastrum capricornutum* (strain 61.81) under static conditions (shake cultures) were exposed for 72 h to concentrations (nominal) from 1.00 to 56.0 mg /L.

Findings:

Test Substance	50 WG
Test Object	*Selenastrum capricornutum*
Exposure	72h, static
ErC_{50} (growth rate) mg as/L	5.52
lowest tested conc. with effect (LOErC) mg as/L	0.89
highest tested conc. without toxic effect (NOErC) mg as/L	0.50
Toxic threshold effect concentration (mean LOEC-NOEC) mg as/L	0.66

Observations: The results are provided in summary form in the Table. Analytical data showed that the measured levels about 99 % of nominal, so nominal values were used in reporting results. The 72-hour ErC_{50} was 5.52 mg as/L. The NOEC and LOEC values were 0.5 and 0.89 mg as/L.

Conclusion: XXXXXX WG 50 is moderately toxicity to *Selenastrum*.

Risk assessment: PEC_i values vary depending on distance from and the depth of the water body. For the use pattern presented in Table 10.1-1 and the distances from water body as well as the resulting drift rates presented in Table 10.2-1, initial concentrations of between 0.45 and 3.75 µg as/L for 1 m and for 30 cm water depth were calculated (*cf* Table 10.2-1). On the basis of the growth rate EC_{50} value for algae (5.52 mg as/L) and the PEC_i value, acute TERs between 12267 and 1472 can be derived.

The algae test is a chronic test with a short term exposure period. Thus the TER_{st} is deemed the appropriate figure for the formal hazard assessment. However, in the case of XXXXXX, the consideration the acute situation demonstrated safety factors high enough to exclude potential risks. Therefore it can be concluded that a more detailed risk assessment is not necessary.

APPENDIX 9

FORMAT FOR THE LISTING OF END POINTS TO BE INCLUDED IN THE *TIER III* OVERALL SUMMARY AND ASSESSMENT [16]

Chapter 1: **Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling**

Active substance (ISO Common Name)	
Function (*e.g.* fungicide)	
Rapporteur Member State	

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	
Chemical name (CA)	
CIPAC No	
CAS No	
EEC No (EINECS or ELINCS)	
FAO Specification (including year of publication)	
Minimum purity of the active substance as manufactured (g/kg)	
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	
Molecular formula	
Molecular mass	
Structural formula	

[16] Other end points will be relevant in particular cases - decisions as to the additional end points to be included can only be made on a case by case basis.

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	
Boiling point (state purity)	
Temperature of decomposition	
Appearance (state purity)	
Relative density (state purity)	
Surface tension	
Vapour pressure (in Pa, state temperature)	
Henry's law constant (Pa m^3 mol^{-1})	
Solubility in water (g/l or mg/l, state temperature)	pH_____:
	pH_____:
	pH_____:
Solubility in organic solvents (in g/l or mg/l, state temperature)	
Partition co-efficient (log P_{OW}) (state pH and temperature)	pH_____:
	pH_____:
	pH_____:
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH_____:
	pH_____:
	pH_____:
Dissociation constant	
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	
Photostability (DT_{50}) (aqueous, sunlight, state pH)	
Quantum yield of direct phototransformation in water at λ > 290 nm	
Flammability	
Explosive properties	

Summary of intended uses

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	
with regard to toxicological data	
with regard to fate and behaviour data	
with regard to ecotoxicological data	

Chapter 2: Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	
Impurities in technical as (principle of method)	
Plant protection product (principle of method)	

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	
Soil (principle of method and LOQ)	
Water (principle of method and LOQ)	
Air (principle of method and LOQ)	
Body fluids and tissues (principle of method and LOQ)	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

Chapter 3: Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption:	
Distribution:	
Potential for accumulation:	
Rate and extent of excretion:	
Metabolism in animals	
Toxicologically significant compounds (animals, plants and environment)	

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	
Rat LD_{50} dermal	
Rat LC_{50} inhalation	
Skin irritation	
Eye irritation	
Skin sensitization (test method used and result)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect	
Lowest relevant oral NOAEL / NOEL	
Lowest relevant dermal NOAEL / NOEL	
Lowest relevant inhalation NOAEL / NOEL	

Genotoxicity (Annex IIA, point 5.4)

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect	
Lowest relevant NOAEL / NOEL	
Carcinogenicity	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	
Lowest relevant reproductive NOAEL / NOEL	
Developmental target / critical effect	
Lowest relevant developmental NOAEL / NOEL	

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

..... |

Other toxicological studies (Annex IIA, point 5.8)

..... |

Medical data (Annex IIA, point 5.9)

..... |

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI			
AOEL			
Drinking water limit			
ARfD (acute reference dose)			

Dermal absorption (Annex IIIA, point 7.3)

..... |

Acceptable exposure scenarios (including method of calculation)

Operator	
Workers	
Bystanders	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Chapter 4: Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	
Rotational crops	
Plant residue definition for monitoring	
Plant residue definition for risk assessment	
Conversion factor (monitoring to risk assessment)	

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	
Animal residue definition for monitoring	
Animal residue definition for risk assessment	
Conversion factor (monitoring to risk assessment)	
Metabolism in rat and ruminant similar (yes/no)	
Fat soluble residue: (yes/no)	

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

.....	

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

.....	

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle			
Liver			
Kidney			
Fat			
Milk			
Eggs			

Appendix 9 Format For The Listing Of End Points to be Included in the Tier III Overall Summary And Assessment

Company name Month and year Active Substance (Name) page of

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

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Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	
TMDI (European Diet) (% ADI)	
NEDI (% ADI)	
Factors included in NEDI	
ARfD	
Acute exposure (% ARfD)	

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studies	Transfer factor	% Transference *

* Calculated on the basis of distribution in the different portions, parts, or products as determined through balance studies

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

.....	
.....	
.....	
.....	
.....	
.....	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

Chapter 5: Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days	
Non-extractable residues after 100 days	
Relevant metabolites - name and/or code, % of applied (range and maximum)	

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation	
Soil photolysis	

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	
Laboratory studies (range or median, with n value, with r^2 value)	DT_{50lab} (20°C, aerobic):
	DT_{90lab} (20°C, aerobic):
	DT_{50lab} (10°C, aerobic):
	DT_{50lab} (20°C, anaerobic):
	degradation in the saturated zone:
Field studies (state location, range or median with n value)	DT_{50f}:
	DT_{90f}:
Soil accumulation and plateau concentration	

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc}	
K_d	
pH dependence (yes / no) (if yes type of dependence)	

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching	
Aged residues leaching	
Lysimeter/ field leaching studies	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

PEC (soil) (Annex IIIA, point 9.1.3)

Method of calculation	
Application rate	

$PEC_{(s)}$	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 24h				
2d				
4d				
Long term 7d				
28d				
50d				
100d				

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	pH_____:
	pH_____:
	pH_____:
Photolytic degradation of active substance and relevant metabolites	
Readily biodegradable (yes/no)	
Degradation in water/sediment - DT_{50} water - DT_{90} water - DT_{50} whole system - DT_{90} whole system	
Mineralization	
Non-extractable residues	
Distribution in water / sediment systems (active substance)	
Distribution in water / sediment systems (metabolites)	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

PEC (surface water) (Annex IIIA, point 9.2.3)

Method of calculation	
Application rate	
Main routes of entry	

$PEC_{(sw)}$	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 24h				
2d				
4d				
Long term 7d				
14d				
21d				
28d				
42d				

PEC (sediment)

Method of calculation	
Application rate	

$PEC_{(sed)}$	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term				
Long term				

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	
Application rate	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

$PEC_{(gw)}$

Maximum concentration	
Average annual concentration	

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air	
Quantum yield of direct phototransformation	
Photochemical oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} .....
Volatilization	from plant surfaces:
	from soil:

PEC (air)

Method of calculation	

$PEC_{(a)}$

Maximum concentration	

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	
Surface water (indicate location and type of study)	
Ground water (indicate location and type of study)	
Air (indicate location and type of study)	

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Chapter 6: Effects on Non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals	
Acute toxicity to birds	
Dietary toxicity to birds	
Reproductive toxicity to birds	

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Laboratory tests				
Microcosm or mesocosm tests				

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger

Bioconcentration

Bioconcentration factor (BCF)	
Annex VI Trigger for the bioconcentration factor	
Clearance time (CT_{50}) (CT_{90})	
Level of residues (%) in organisms after the 14 day depuration phase	

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity	
Acute contact toxicity	

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				

Field or semi-field tests

Appendix 9 **Format For The Listing Of End Points to be Included in the *Tier III* Overall Summary And Assessment**

Company name **Month and year** **Active Substance (Name)** **page of**

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests						

Field or semi-field tests

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity	
Reproductive toxicity	

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization	
Carbon mineralization	

APPENDIX 10

FORMAT FOR THE COMPILATION OF *TIER III* SUMMARIES AND OVERALL ASSESSMENTS

1.1 ***Identity***

All the Annex IIA points (active substance) and IIIA points (XXXX1, XXXX2 and XXXX3 formulations) concerned have been addressed in the relevant *Tier II* Section 1 summaries.

1.2 ***Physical and chemical properties***

XXXX is an abc fungicide which can be formulated as an emulsifiable concentrate, suspension concentrate or wettable powder. Data submitted on the active substance show no evidence of adverse physical and chemical properties although the compound is highly photolabile in air and aqueous media. Data submitted on the formulations indicate that they are stable under the accelerated storage conditions used (*i.e.* do not appear to be photolabile as formulated products in commercial packaging) although no data on shelf life are presently available.

1.3 ***Details of uses and further information***

All the Annex IIA and IIIA points concerned have been addressed in the *Tier II* Section 1 summaries.

1.4 ***Classification and labelling***

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2 ***Methods of analysis***

Adequate methodology exists for the determination of XXXX in the technical substance, plant protection products, plants, soil, water and products of animal origin. Full details are provided in section 2 of the Annex II and Annex III *Tier II* summaries. Some further data on the validation of these methods is required.

3 ***Impact on human and animal health***

3.1 *Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products*

XXXX and/or its metabolites have been shown to be rapidly and extensively absorbed, metabolised, distributed and eliminated, following oral gavage dosing of rats. Elimination was principally in the faeces as a result of biliary excretion. XXXX was poorly absorbed dermally in monkeys, but was slightly better absorbed from formulations tested in rabbits. There would appear to be a number of metabolic pathways yielding a large number of metabolites (see Figure 1).

Figure 1 **Metabolic pathways for XXXX in animals, plants, soil and water**

(*pro memoria*)

XXXX is of low acute toxicity by the oral and dermal routes. XXXX may also be of low acute toxicity by the inhalation route but the available evidence is not conclusive. The acute oral LD_{50} value was **** mg/kg bw for rats and > **** mg/kg bw for mice. The acute dermal LD_{50} value was > **** mg/kg bw for rabbits. No deaths or overt signs of toxicity were noted in rats exposed (nose only) to a solid particulate aerosol of * mg/l (mass median aerodynamic diameter of 12 μm).

In according with the EU classification criteria, XXXX is neither a skin nor eye irritant - standard tests with rabbits. It was found not to be a skin sensitizer when tested using the maximisation method of Magnusson and Klingman.

Following repeated dietary exposure of rats for 3 months, there was some evidence of toxicity (slightly reduced body weight gain in males and slightly increased fatty change in some animals) at the highest dose tested, **** ppm. There was also evidence of hepatic enzyme induction at lower dose levels. The overall NOAEL was *** ppm (equivalent to approximately *** mg/kg bw/day).

Histological evidence of toxic effects in the liver and kidney (principally fatty change) was observed, as well as hepatic enzyme induction was observed in mice, following dietary administration of up to **** ppm XXXX for 3 months. On the basis of histological evidence of hepatic toxicity at *** ppm and above, the NOAEL was found to be *** ppm (equivalent to approximately ** mg/kg bw/day).

XXXX was administered orally in gelatine capsules to dogs for up to 12 months. No evidence of systemic toxicity was seen when doses up to ** mg/kg bw/day were administered for 3 months. Following administration of up to *** mg/kg bw/day for 12 months the principal adverse finding was mild bile stasis in a small number of dogs at the top dose, an effect which was still present at the end of the 3-month recovery period. There was also evidence of hepatic enzyme induction in animals administered with *** mg/kg bw/day. The NOAEL in the 12 month dog study was *** mg/kg bw/day.

Following repeated dermal application of **** mg/kg bw/day to rabbits for 21 consecutive days, no treatment related adverse systemic effects, or effects at the site of application, were noted.

Long-term toxicity and carcinogenicity studies were conducted in rats and mice. The liver was found to be the principle target organ, with fatty change being the main finding. Rats were the more sensitive species with an overall NOAEL for rats of ** ppm (equivalent to *** mg/kg bw/day), in contrast to the NOAEL for mice of *** ppm (equivalent to approximately ** mg/kg bw/day). On the basis of the carcinogenicity studies reported, there is no evidence that XXXX is tumorigenic in rats or mice.

The genotoxic potential of XXXX was investigated in a comprehensive range of *in vitro* and *in vivo* assays. Although some of the studies were not conducted in accordance with current requirements and standards, on the basis of the overall weight of evidence, it can be concluded that XXXX is not genotoxic.

In single/multi-generation studies, no adverse effects on reproduction were observed in either rats or mice. In the rat studies, the NOAEL was found to be ** ppm (equivalent to approximately * mg/kg bw/day) and in the mice studies the NOAEL was found to be ** ppm (equivalent to approximately * mg/kg bw/day).

The only human toxicology information available is that derived from an evaluation of the medical records of ** employees involved in the manufacture of XXXX. There was no evidence of adverse health effects as a result of potential exposure to XXXX, apart from three cases of transient rashes from skin contact and one case of transient nausea and vomiting following accidental ingestion. The cases resolved without evidence of residual medical effects.

3.2 *ADI*

In order to set an acceptable daily intake (ADI) for XXXX it is relevant to consider that although there is clear evidence of systemic toxicity in animals, as a result of prolonged dietary exposure, with the liver being the target organ, there is no evidence that XXXX is genotoxic or tumorigenic or toxic to reproduction.

No suitable human data are available which would serve as a basis for setting an ADI.

In chronic exposure dietary studies with rats and mice, rats were the more sensitive species. The overall NOAEL for rats in the chronic studies appeared to be ** ppm, equivalent to ** mg/kg bw/day - based on increased fatty liver at ** ppm, the next highest dose level tested.

It is appropriate to apply an uncertainty factor of 100 to the NOAEL of ** mg/kg bw/day and thus derive an ADI for XXXX of *** mg/kg bw.

3.3 *AOEL*

The plant protection products XXXX1, XXXX2 and XXXX3 are to be applied by mistblower or hydraulic sprayer. Such means of application are likely to lead to exposure of operators by the dermal route predominantly and to a lesser extent by the inhalation route. Exposure by inhalation is not likely to result in significant, secondary oral exposure. The exposure of operators is likely to occur repeatedly, but not persistently, throughout their life-time.

Oral absorption of XXXX was extensive in rats at a relevant dose level (** % absorption within 24 h of a single oral dose of * mg/kg bw/day). Accordingly no adjustment of any AOEL proposed is necessary to take this factor into account.

No suitable human data are available on which to base and AOEL.

A repeated exposure dermal study with rabbits exposed to **** mg/kg bw/day is available. However, the value of using a dermal study to set a systemic AOEL can be questioned. Since there was no clear evidence of a compound related effect following dermal exposure for only 21 days, and adverse effects (including developmental toxicity) have been seen following subacute/ subchronic oral exposure, it is not appropriate to use this dermal study as a basis for setting an AOEL.

The lowest NOAEL determined following subacute/subchronic oral exposure was that observed in a 12-month dog study (*** mg/kg bw/day). Bearing in mind the nature of the adverse effects seen in this study (principally mild bile stasis), it is considered appropriate to apply a 100-fold uncertainty factor to the NOAEL, thereby deriving a short term AOEL for XXXX of ** mg/kg bw/day.

3.4 *ARfD*

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3.5 *Drinking water limit*

No suitable human data are available and there are no chronic exposure animal studies in which XXXX has been administered in drinking water. The maximum allowable concentration (MAC) in drinking water therefore should be based on the ADI derived from dietary studies.

In order to calculate the MAC for drinking water it is appropriate to divide the ADI by an additional uncertainty factor of 10 and thus derive a daily intake of **** mg/kg bw. The International Programme on Chemical Safety (WHO, 1994) proposed that for risk assessment purposes, a reference human be considered to weigh 64 kg and to have a daily intake of drinking water of 1.4 litres. Hence, a daily intake of **** mg XXXX/kg bw would be achieved by 64 kg human consuming ** litre drinking water/day containing **** mg XXXX/litre. Thus a MAC for XXXX in drinking water of ** µg/l is derived.]

3.6 *Impact on human or animal health arising from exposure to the active substance or to impurities contained in it*

3.6.1 Operators, bystanders and workers.

3.6.1.1 Exposure as a proportion of the AOEL, UK model.

Plant Protection Product/ Application method	**Total systemic exposure 60 kg person (mg/kg bw/day)**		**% of AOEL**	
	no PPE worn	**PPE worn[1]**	**no PPE worn**	**PPE worn[1]**
XXXX1				
Orchard Broadcast Air Assisted Spray	***	***	**	**
Hand Held Sprayer - low level crop	***	***	**	**
Field Crop Sprayer	***	***	**	**
XXXX2				
Orchard Broadcast Air Assisted Sprayer	***	***[2]	**	**[2]
Hand Held Sprayer - low level crop	***	***[2]	**	**[2]
Field Crop Sprayer	***	****[2]	**	*[2]
XXXX3				
Orchard Broadcast Air Assisted Sprayer	***	***[2]	***	**[2]
Hand Held Sprayer - low level crop	***	***	***	**
Field Crop Sprayer	***	****	***	*

[1] PPE is gloves during mixing/loading only unless where indicated otherwise

[2] Gloves worn during application as well as mix/loading

Appendix 10 **Format for the Compilation of *Tier III* Summaries and Overall Assessments**

Company name **Month and year** **Active Substance (Name)** **page of**

3.6.1.2 Exposure as a proportion of the AOEL, German model

Plant Protection Product/ Application Method	Total systemic exposure 60 kg person		% of AOEL	
	no PPE worn	PPE worn[1]	no PPE worn	PPE worn[1]
XXXX1				
Tree Broadcast Air Assisted Sprayer	***	**** [2]	**	* [2]
Hand Held Sprayer - high level crop	***	****	**	*
Field Crop Sprayer	***	***	**	**
XXXX2				
Tree Broadcast Air Assisted Sprayer	***	**** [2]	**	* [2]
Hand Held Sprayer - high level crop	***	****	**	*
Field Crop Sprayer	***	****	**	*
XXXX3				
Tree Broadcast Air Assisted Sprayer	***	*** [2]	**	** [2]
Hand Held Sprayer - high level crop	***	****	**	*
Field Crop Sprayer	***	****	**	*

[1] PPE is gloves during mixing/loading only unless where indicated otherwise

[2] "Coverall" and sturdy footwear worn during application

The operator exposure estimates generated using the UK and German models, generally indicate that the short term AOEL (** mg/kg bw/day) will not be exceeded during mixing, loading and application of XXXX1, XXXX2 and XXXX3 even when no PPE is worn. An exception is the exposure estimated in the orchard sprayer use of XXXX1 which, using the UK model, is predicted to exceed the short term AOEL by up to * times. Significant dermal exposure occurs during application in orchards using vehicles without cabs. If the German model is used, the reduction in potential dermal exposure provided by wearing a coverall is sufficient to reduce the estimate of actual dermal exposure (and hence total systemic exposure) to a level below the AOEL. The UK model does not have the facility to take account of the effect of the use of coveralls, but the protection afforded by the use of protective gloves is predicted to be sufficient to reduce exposure to a level below the AOEL. The use of coveralls (the use of which is recommended with the use of gloves) would reduce exposure still further.

The UK model outdoor low level knapsack data set is not appropriate for the estimation of exposure associated with applications to tomato plants, and similar crops, since the higher level of the target is likely to increase the amount of potential exposure, and since there is also a potential for exposure resulting from contact with treated foliage, an aspect that is not addressed by the model. Similarly, estimates made using the German model high level crop hand held sprayer scenario do not provide an estimate of exposure likely in application to tomatoes in protected cropping situations. The high level crop hand held sprayer scenario relates to hand held mist blower equipment. A data base on

exposure levels associated with application to protected crops (glass houses or polythene tunnels) is not available for use with either the UK or German models.

Reports of studies in which operator exposure levels were measured during application to grapes and apples in the USA, and during use on glasshouse grown roses in both the USA and UK, were submitted.

The predicted systemic exposure of operators not wearing PPE applying XXXX1 to grapes was at or below the short term AOEL (** mg/kg bw/day). From studies using XXXX2 systemic exposure of operators applying XXXX2 to grapes, and apples were predicted to be at or below the short term AOEL when no PPE was worn, or to be below ** % of the AOEL when gloves were worn during mixing and loading. These conclusions are based on the assumption that mixing, loading and spraying continues for a full day and the assumption that large areas are covered. The studies reported relating to glasshouse grown roses, showed that the systemic exposure of operators was below the short term AOEL when gloves were used for mixing and loading. Therefore it can be concluded that the risks to operators associated with these uses are at acceptable levels.

The predicted levels of exposure of bystanders present outside the treatment area, as a result of either contact with spray drift during application or contact with airborne XXXX after application, are below the short term AOEL (** mg/kg bw/day), and therefore the potential risk is considered to be at an acceptable level.

Predicted levels of exposure of workers re-entering treated crops, estimated on the basis of the estimates of initial levels of dislodgeable foliar residues (DFR) present, were such that levels of exposure of workers in both tomatoes and ornamental crops are at acceptable levels. The upper limits of the ranges of predicted exposures of workers in grapes and apples were *-* times higher that the short term AOEL (** mg/kg bw/day). However, actual measurements of exposure of workers trimming table grapes and harvesting apples in the USA indicated that exposures will be below the level of the short term AOEL (** mg/kg bw/day) (see point 7.2.3 for further details).

3.6.2 Consumers

The estimated consumer intake levels do not exceed the proposed ADI of *** mg/kg bw/day. It can therefore be concluded that acceptable margins of safety exist for consumers. A further assessment of consumer intake levels, using proposed and adopted MRLs will be necessary as additional uses are proposed (TMDI calculations). (see Section 7.1.2 for further details)

4 *Residues*

4.1 *Definition of the residue relevant to MRLs*

Based on the metabolism data submitted for certain plants and domestic animals (where XXXX was the main component present or was present at levels which are appropriate for monitoring), residues for plants, plant products and products of animal origin should be defined in terms of XXXX alone.

4.2 *Residues relevant to consumer safety*

4.2.1 Nature and levels of residues

In both apples and grapes, XXXX was metabolised to give a large number of metabolites which were present at very low levels. It is considered highly likely that these metabolites are photodegradation products as they generally show very similar chromatographic properties to the products of photodegradation of XXXX in aqueous systems. The major metabolic product in apples, grapes and cucumbers was XXXXx.

In goats, a number of metabolites which were not detected in rats were formed. These occurred at very low levels and would be unlikely to be present at levels > *** mg/kg following feeding of apple pomace to domestic animals which had been treated according to current GAP. XXXX was also detected in liver and kidney samples at low levels. In pigs, the major metabolic product was found to be XXXXx. The identity of metabolites formed in chickens was not determined. Current GAP is such that it is not likely that there could be significant intakes of XXXX (*i.e.* >** mg/kg diet) by poultry.

Based on the metabolism data submitted for certain plants and domestic animals (where XXXX was the main component present or was present at levels which are appropriate for monitoring), residues for plants, plant products and products of animal origin should be defined in terms of XXXX alone.

Sufficient residue data were not submitted - further data are required to permit proposals to be made for the establishment of MRLs. The highest residues detected in the residue trials reported was used to calculate theoretical consumer intakes.

Residues present in wine, grapes and cherries were found to be stable for at least ***, *** and *** days, respectively, following storage at -20°C. On the basis of extrapolation to other relevant crops, it can be assumed that residues of XXXX are stable at -20°C in other crops within the group of 'fruiting crops' (metabolism studies).

Data provided with respect to the effects of processing on residues, demonstrated that there will be no adverse effects for consumer safety as a result of concentration processes.

Cattle and pigs were fed for ** days at various rates including a rate equivalent to ** N for cattle (* mg/kg diet) (apple pomace is not fed to other domestic animals). At this dose, residues of XXXX in all tissue except liver were ≤ *** mg/kg. Residues in liver reached a maximum level of *** mg/kg. On the basis of the available residue data, it is apparent that intakes by domestic animals are likely to be low (*ca.* ** mg/kg diet/day) although residue data for all contributors to animal diet are not currently available (peas and pea haulm).

4.2.2 Dietary exposure of consumers

Consumer intake levels were estimated using the highest levels recorded in currently available supervised trials conducted in accordance with the critical GAP identified. Using the UK total dietary model and the WHO standard European diet, intakes were calculated to be ≤ ***** mg/kg bw/day (UK diet) and < ***** mg/kg bw/day (WHO standard European diet). Dietary intake levels resulting from any individual crop (based on the UK dietary model) were estimated to be ≤ ***** mg/kg bw/day. Full details of these estimates are provided in Section 4 of the *Tier II* summary of the Annex II dossier provided.

The estimated intake levels do not exceed the proposed ADI of *** mg/kg bw/day. It can therefore be concluded that acceptable safety margins exist for consumers. A further assessment using proposed and adopted MRLs is necessary and should be conducted once the additional residue data necessary to support such MRLs are available (TMDI calculations).

On the basis of the available residue data, it is clear that intake by domestic animals will be low (*ca.* *.* mg/kg diet/day).

4.3 *Residues relevant to worker safety*

4.3.1 Exposure estimates for workers from dislodgeable foliar residues (DFR)

Crop	DFR mg/cm^2	Transfer factor cm^2/hr	Potential dermal exposure mg/kg bw/day	Systemic exposure mg/kg bw/day	% AOEL (** mg/kg bw/day)
Apple	***** (max)[1]	**** (min)	***	***	** %
		***** max)	**	***	*** %
Grape	***** (max)[1]	***** (min)	***	****	** %
		****** (max)	**	***	*** %
Tomato	*****[1]	*** (min)	*****	******	** %
		**** (max)	****	*****	* %
Ornamentals	*****[2]	****	***	****	** %

[1] Based on maximum Day 0 residues from multiple treatments (which are higher than estimates 1 and 2)

[2] Estimate 4, above (which is higher than estimate 3)

The calculated potential dermal exposures are based on the predicted DFR immediately following application. It can be expected that the level of the potential dermal exposure falls as a result of loss of DFR over time following application, as the residue level declines. However, repeat applications are likely. Therefore the level of DFR may be dependent on the DFR remaining from previous applications. This is taken into account where the maximum Day 0 residues are used as the basis of the estimate of DFR. The estimate for ornamentals is for a single application.

These estimates, which can only be regarded as being approximate indications, suggest that:

(i) immediately following application predicted systemic exposures for workers in tomatoes and ornamental crops are below the AOEL (** mg/kg bw/day); and

(ii) exposure for workers in apple and grape crops ranges from less than twice the AOEL for apples and from less than to about 5 times the AOEL for grapes.

4.4 *Proposed EU MRLs and compliance with existing EU MRLs*

4.5 *Proposed EU import tolerances and compliance with existing EU import tolerances*

4.6 *Basis for differences, if any, in conclusions reached having regard to established or proposed CAC MRLs*

5 *Fate and behaviour in the environment*

5.1 *Definition of the residue relevant to the environment*

In soil, residues consist primarily of the parent compound. The levels of extractable metabolites and non-extractable residues formed are likely to be low. Due to the slow rates of degradation of XXXX the compound persists in soil (DT_{90} > * y). A considerable number of different metabolites are formed, none of which are individually considered to be significant. The residue should be defined in terms of XXXX alone.

5.2 *Fate and behaviour in soil*

XXXX is persistent in soil. In laboratory studies at **-**°C first order DT_{50lab} values were ***-**** days. Shorter values were obtained in six field dissipation studies conducted in Germany and although some anomalies occurred which reduce the confidence that can be placed on the DT_{50} field values (**-*** days), it can be concluded that $DT_{90field}$ is more than one year, thus exceeding the Annex VI trigger. Photolysis was shown to occur at the soil surface but the rate of photolysis was not determined. Since XXXX is to be applied after a crop canopy has formed, photolysis is not considered to be a significant mechanism for subsequent degradation in soil.

Annual applications of XXXX could be as high as * kg as/ha (XXXX2) on turf which would give an initial PEC_{soil} of *** mg/kg if it is assumed that all of the applied XXXX reached the soil. In horticulture annual applications could be **** g as/ha (XXXX1) in apple orchards but would be rather lower on other crops. If it is assumed that no interception of XXXX by apple trees or by any ground cover occurs (orchards may not have a large amount of grass cover) initial PEC values in soil could be as high as *** mg/kg. Based on these PECs and degradation rates, concentrations in the soil would reach a plateau of *ca* * mg/kg and *ca* ** mg/kg for horticultural and turf use respectively after approximately four years. It is submitted that on the basis of these predictions it is apparent that long-term concentrations in soil will be low and accumulation will not occur and that therefor a field accumulation study is not required.

5.3 *Fate and behaviour in water*

5.3.1 Groundwater

On the basis of sorption (Koc ***-***) and column leaching (no significant radioactivity was leached from columns of fresh or aged residues) studies provided, it is clear that the mobility in soil of XXXX is low under laboratory conditions. In field dissipation studies one depth segment only was analysed and, hence, no conclusions could be drawn concerning vertical movement of XXXX. Despite its long DT_{50} value, on the basis of computer simulations and expert judgement it is suggested that no movement to groundwater will occur following any of the uses proposed. This conclusion is consistent with the low risk use pattern for XXXX *i.e.* use occurs only in summer to crops with established canopies.

5.3.2 Surface water

XXXX does not hydrolyse but is somewhat photolabile (half life ** day). The significance of aqueous photolysis is generally considered to be low in turbid waters and as XXXX also partitions rapidly into sediment (partition DT_{50} in water << * day) the likelihood of significant degradation by photolysis is not high. However, whether removal is by photolytic degradation or partitioning to sediment, it is concluded that XXXX will not persist in water. Initial PEC values in surface water were determined on the basis of overspray of a single application and were calculated to be ** µg/l from field crop uses, ** µg/l for orchard uses and ** mg/l for use on turf. Over ** days these levels could be expected to decrease to ** ng/l, ** ng/l and ** ng/l respectively. These values are based on direct overspray of the highest application rate proposed and will therefore be reduced for other uses or if a buffer zone is required. The conclusion reached through a simulation study was that run-off water would not contain > ** % of the applied dose and hence erosion and run-off are not likely to be a major route of contamination of watercourses. Studies have shown that once in sediment, XXXX remains extractable. Little degradation occurring over ** days.

5.4 *Fate and behaviour in air*

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6 ***Effects on non-target species***

6.1 *Effects on terrestrial vertebrates*

Exposure of birds and mammals to XXXX is considered to arise mainly from feeding either on grass or fruit treated with XXXX or by feeding on XXXX contaminated insects or earthworms present in XXXX treated crops. XXXX was generally of low toxicity to birds (LD_{50} > **** mg as/kg bw) and mammals (LD_{50} **** mg as/kg bw) and consequently the TER values were greater than the 91/414/EEC Annex VI triggers for unacceptable effects. It can therefore be concluded that the use of XXXX presents a low acute risk to wild birds and mammals.

Exposure of reproducing birds to XXXX is considered to only occur as a result of the multiple applications made in orchards throughout the year. Since the NOEC determined in reproductive toxicity testing was *** mg/kg, the reproductive TER value is above the 91/414/EEC trigger (5) for

unacceptable effects. It can therefore be concluded that the risk to reproducing birds from the use of XXXX in orchards is low.

6.2 *Effects on aquatic species*

Technical XXXX and preparations containing XXXX were of moderate acute toxicity to aquatic organisms with LC/EC_{50} values of *** mg as/l, *** mg as/l and *** mg as/l for the most sensitive fish, aquatic invertebrate and algal species tested, respectively. Worst case assessments (overspray) showed that there was an acute risk (TER < ***) to all 3 aquatic groups associated with the use of XXXX, particularly its uses on turf and in orchards. However, on the basis of a spray drift assessment, it was evident that the risk to aquatic life associated with use on turf was acceptable, particularly when a DT_{50} of approx. * day for XXXX in the aqueous phase of water/sediment systems was taken into account. Although a spray drift assessment indicated that the acute risks to fish and algae associated with the remaining agricultural/horticultural uses were acceptable, an acute risk to aquatic invertebrates was identified for air assisted spray application such as those made in orchards. Consequently, a 15m buffer zone restriction around watercourses is recommended for air assisted spray applications of the formulation to tree/bush crops.

XXXX was of moderate chronic toxicity to fish and aquatic invertebrates with NOECs of **** mg as/l and **** mg as/l respectively. On the basis of worst case overspray assessments, it became apparent that there was a chronic risk (TER <10) to fish and aquatic invertebrates associated with use of XXXX on turf and with the agricultural/horticultural uses of XXXX. The more serious risks were associated with its use on turf and in orchards. An assessment conducted to assess the risks associated with spray drift showed that risk associated with chronic exposure to both fish and aquatic invertebrates resulting from use on turf use was acceptable, particularly when the DT_{50} of approx. * day for XXXX in the aqueous phase of water/sediment systems was taken into account. XXXX did not present a bioaccumulation risk since the fish maximum BCF was *** and DT_{50} for XXXX in the aqueous phase of water/sediment systems was approx. * day.

Although XXXX was rapidly removed from the aqueous phase of natural sediment water systems, it was found to partition and persist in the sediment phase of such water sediment systems. An overspray and a spray drift assessment carried out using *Daphnia magna* toxicity data as an indicator of the potential toxicity of XXXX to sediment dwelling invertebrates indicated that there may be a chronic risk to sediment dwelling invertebrates associated with the use of XXXX by air assisted spray application to tree/bush crops such as orchards. Therefore, a study to permit assessment of the chronic toxicity of XXXX has been initiated (to be submitted in June ****). Pending the assessment of that study, a 15m buffer zone restriction around watercourses is proposed for application of XXXX to tree/bush fruit using air assisted spray applications equipment.

6.3 *Effects on bees and other arthropod species*

XXXX was of low acute toxicity to honeybees with acute oral and contact LD_{50} values of > ** and > *** µg as/bee respectively. Although the hazard quotients associated with use on turf (< ***) may have exceeded the Annex VI trigger of 50, the risk to bees was considered to be low, given the timing of applications - mainly in winter/autumn when bees were unlikely to be foraging. The hazard quotients associated with the remaining uses were below 50 indicating a low risk to bees.

Data are not presently available which satisfy the Annex II and III non-target arthropod data requirements. Therefore, non-target arthropod toxicity data will be supplied in line with the current Annex II and III data requirements (to be submitted in June ****).

6.4 *Effects on earthworms and other soil macro-organisms*

XXXX was of moderate toxicity to earthworms with an acute LC_{50} value of **-** mg as/kg soil and a reproductive NOEC of **** g as/ha. On the basis of multiple overspray assessments, the acute and sub-lethal risk to earthworms associated with both the worst case turf (maximum application rate) and orchard (maximum multiple applications) uses, was considered to be low. On the basis of the low risk associated with use of XXXX for earthworms and soil micro-organisms (below), the risk to other soil macro-organisms is also considered to be low.

6.5 *Effects on soil micro-organisms*

The data provided showed that XXXX elicited no effect of XXXX on soil respiration and nitrification processes at application rates of up to ** times the maximum recommended application rate. On the basis of the worst case exposure scenarios for turf and orchard uses (representative of worst case multiple oversprays at maximum application rate) of XXXX as exposure estimates, it is clear the risk to soil micro-organisms associated with use of XXXX is low.

6.6 *Effects on other non-target organisms (flora and fauna)*

No data are available. It is suggested data on the effects of XXXX on other non-target organisms (flora and fauna) are not necessary.

6.7 *Effects on biological methods of sewage treatment*

It is not considered likely that the normal use of XXXX will result in contamination of sewage treatment plants. However, data were submitted which indicated that XXXX at concentrations up to **** ppm had no effect on sewage treatment processes. This indicates that the risk to sewage treatment processes from the use of XXXX is considered low.

Appendix 10 **Format for the Compilation of *Tier III* Summaries and Overall Assessments**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

Overall conclusions

An ADI of 0.01 mg/kg bw/day is proposed.

An AOEL of 0.1 mg/kg bw/day, based on short-term exposure, is proposed.

A drinking water limit - maximum allowable concentration (MAC) - 0.05 mg/l is proposed.

It is expected that residues of XXXX, consequent on application consistent with good plant protection practice, will not have harmful effects on human or animal health or on groundwater or any unacceptable influence on the environment. Such residues can be measured by methods using conventional analytical equipment. Some further data are required to confirm this assessment.

The following provisional EU MRLs are proposed:-

cereals	*** mg/kg	solanacea	*** mg/kg
citrus fruit	*** mg/kg	cucurbits (edible peel)	*** mg/kg
bulb vegetables	*** mg/kg	cucurbits (inedible peel)	*** mg/kg
leafy vegetables	*** mg/kg	root and tuber vegetables	*** mg/kg
flowering brassicas	*** mg/kg	potatoes	*** mg/kg
head brassicas	*** mg/kg	pulses	*** mg/kg
leafy brassicas	*** mg/kg	oil seeds	*** mg/kg

The following import tolerances are proposed:-

bananas	*** mg/kg	tea	*** mg/kg

It is expected that the use of XXXX, consistent with good plant protection practice, will not have any harmful effects of human or animal health or any unacceptable effects on the environment. However some further data are required to confirm this assessment.

Proposed decision

It is proposed that XXXX be included in Annex I of Council Directive 91/414/EEC and that the inclusion be conditional on:-

(i) a minimum purity of 95 %; and

(ii) the tests and studies listed below being provided by the dates specified.

It is also proposed that the following restriction be associated with the inclusion of XXXX in Annex I of Council Directive 91/414/EEC:-

> that authorizations granted for preparations containing XXXX, which permit application by means of air assisted spray application equipment to bush or tree crops, require the maintenance of a 15m buffer zone between water courses, drains and treated areas.

Further information to be submitted

The following data will be provided within ..... months.

Physical, chemical properties

(i) UV/VIS spectra of pure XXXX, molecular extinction at relevant wavelengths (IIA 2.5)

(ii) solubility in organic solvents (IIA 2.7)

Methods of analysis

(i) repeatability data for the determination of XXXX in technical material and plant protection products (Annex IIA 4.1.3.4; Annex IIIA 5.1.3.4)

(ii) confirmation of the identity of XXXX residues in all substrates (specificity) (Annex IIA 4.2.1; Annex IIIA 5.2)

iii) method for determining the presence of the xxxxx isomer of XXXX in the active substance as manufactured (annex IIA 4.1.2)

Residues data for the crops as indicated below (IIA 6.3)

Crop	GAP (N/S)	Recommendation
Pears	S	Further data required to support critical GAP (14 day PHI) (x trials)
Peaches	N	No GAP
	S	Data from x trials supports GAP. Further data required (x trials)
Cherries	N	Further data required (x trials)
	S	No GAP
Wine grapes	N	Data from x trials support GAP. Further data required (x trials)
	S	Further data required to assess whether S GAP could give rise to higher levels than N GAP. Since GAP for table grapes is identical these data will be submitted to support this use.
Table grapes	N	Further data required. Data from N GAP wine grapes will be used to support this GAP since PHI has little effect on XXXX residues in grapes.
	S	Further data required. Since GAP for wine grapes is identical these data will be submitted to support use.
Strawberries	N	Further data required (x trials)
	S	Further data required (extrapolation between NMS and SMS GAP proposed)
Raspberries	N	Further data required (x trials)
	S	No GAP
Currants	N	Further data required (x trials)
	S	No GAP

Appendix 10 **Format for the Compilation of *Tier III* Summaries and Overall Assessments**

Company name	**Month and year**	**Active Substance (Name)**	**page of**

Effects on non-target species

(i) Study on the toxicity of XXXX to both *Aphidius rhopalosiphi* and *Typhlodromus pyri* using application rates relevant to the maximum approved application rate (IIA 8.3.2)

(ii) Study on the toxicity of XXXX to both a ground dwelling predator species and a foliage dwelling species at the relevant maximum recommended application rates for both the arable and horticultural uses of XXXX (IIA 8.3.2)

(iii) Extended laboratory or semi-field/field studies on the effect of multiple applications of XXXX on non-target arthropods in orchards. This study must reflect the proposed conditions of use (*e.g.* max application rate, minimum re-application interval). (IIA 8.3.2)

(iv) Laboratory study to investigate the risks associated with chronic exposure of sediment dwelling invertebrates (*e.g.* Chironomid sp.) resulting from application of XXXX by means of air assisted spray equipment to tree/bush crops. (IIA 8.2.7)

A listing of the end points relevant to the active substance, presented in the format specified in Appendix 9, should be attached to each *Tier III* Summary and Overall Assessment submitted.

APPENDIX 11

FORMS FOR USE IN CHECKING DOSSIERS FOR COMPLETENESS

Part 1 **Evaluation Form 1 -**

for use in checking that the required supporting documentation has been provided

Active substance:
Applicant:
Date:

Document	Description of the document - circumstances in which required	Document provided Y/N#	Official use only * Data Gap Y/N#
A	Statement of the context in which the dossier is submitted - always required	—	—
B	Documentation relating to the joint submission of dossiers -		
	* Claim that all reasonable steps were taken	—	—
	* Documentation to support the claim made	—	—
	- required for existing active substances for which there is more than one notifier, where a joint dossier was not submitted by all notifiers		
C	Existing or proposed labels, and where relevant leaflets for each preparation for which an Annex III dossier is submitted - required where requested	—	—
	Existing or proposed labels relevant to the uses on the basis of which existing MRLs or import tolerances are supported or new MRLs or import tolerances are proposed - required where requested	—	—
D-1	Details of intended uses (supported by the applicant and for which data are provided or are to be provided) and the conditions of use, on food and feed crops, and on non food and feed crops, in the territory of the EU, presented using the appropriate form - always required	—	—
D-2	A list of the authorized uses in the EU, an indication of whether actually used and of the extent of use, presented using the appropriate form - required for existing active substances	—	—
D-3	Details of the intented uses (supported by the applicant and for which data are provided or are to be provided) and conditions of use (GAPs) in exporting countries, for which import tolerances are required, presented using the appropriate form - required for food or feed crops which are imported in significant quantities into the territory of the EU	—	—

* To be completed by the Competent Authority of the Member State to which application is made

\# Y = yes; N = no

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 1** **Evaluation Form 1 Supporting Documentation**

Active substance: **Applicant:** **Date:**

Document	Description of the document - circumstances in which required	Document provided Y/N	Official use only Data Gap Y/N
E-1	Listing of EU MRLs, presented using the appropriate form - required for existing active substances	—	—
	Listing of MRLs established by Member States, presented using the appropriate form - required for existing active substances	—	—
E-2	Listing of MRLs established in exporting countries, presented using the appropriate form - required where an import tolerance is proposed	—	—
	Listing of MRLs in non-EU OECD countries, presented using the appropriate form - required where an import tolerance is proposed	—	—
F	A copy of each notification submitted to the Commission - required for existing active substances	—	—
G	Whether permitted in food, animal feeding stuffs, medicines or cosmetics in accordance with EU legislation - required for each formulant unless an Annex II dossier is provided for the formulant	—	—
H	Safety data sheet prepared in accordance with Directive 67/548/EEC - required for each formulant	—	—
I	Other available toxicological and environmental data on the formulant - required if requested	—	—
J	Confidential data and information, to include -		
	* A listing of the data and information for which confidentiality is requested, cross referenced to the relevant test and study reports, dossier summaries and supporting documentation - always required	—	—
	* A justification for the claim to confidentiality for each item for which confidentiality is requested - always required	—	—
	* Highlighting of information contained in relevant study reports, dossier summaries and supporting documentation - required where the information concerned is provided in those documents	—	—
	* File containing confidential data and information - optional requirement	—	—

Part 2 **Evaluation Form 2 -**

for use in checking that the required Annex II and Annex III dossier summaries and an overall assessment, have been provided

Active substance:

Applicant:

Date:

Document	Description of the document - circumstances in which required	Document provided Y/N#	Official use only * Data Gap Y/N#
L-II	Annex II, *Tier I* reports as to the quality of individual test and study reports - always required	—	—
L (Reference List)	Listing of test and study reports, test guidelines and published papers relevant to the Annex II dossier:-		
	- papers and reports submitted listed by Annex point	—	—
	- papers and reports submitted listed by alphabetically by author	—	—
	- list of papers and reports not submitted, arranged alphabetically by author	—	—
	- always required		
M-II	Annex II, *Tier II* dossier summary and overall assessment - always required	—	—
L-III	Annex III, *Tier I* reports as to the quality of individual test and study reports for each Annex III dossier submitted - always required		
	* First preparation	—	—
	* Second preparation	—	—
	* Third preparation	—	—
	* Fourth preparation	—	—
L (Reference List)	Listing of test and study reports, test guidelines and published papers relevant to each Annex III dossier - always required		
	* First preparation		
	- papers and reports submitted listed by Annex point	—	—
	- papers and reports submitted listed by alphabetically by author	—	—
	- list of papers and reports not submitted, arranged alphabetically by author	—	—
	* Second preparation		
	- papers and reports submitted listed by Annex point	—	—
	- papers and reports submitted listed by alphabetically by author	—	—
	- list of papers and reports not submitted, arranged alphabetically by author	—	—

* To be completed by the Competent Authority of the Member State to which application is made

\# Y = yes; N = no

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 2** **Evaluation Form 2 Dossier Summaries and Overall Assessment**

Active substance: **Applicant:** **Date:**

Document	Description of the document - circumstances in which required	Document provided Y/N	Official use only Data Gap Y/N
	* Third preparation		
	- papers and reports submitted listed by Annex point	—	—
	- papers and reports submitted listed by alphabetically by author	—	—
	- list of papers and reports not submitted, arranged alphabetically by author	—	—
	* Fourth preparation		
	- papers and reports submitted listed by Annex point	—	—
	- papers and reports submitted listed by alphabetically by author	—	—
	- list of papers and reports not submitted, arranged alphabetically by author	—	—
M-III	Annex III, *Tier II* dossier summary and overall assessment - always required		
	* First preparation		
	* Second preparation	—	—
	* Third preparation	—	—
	* Fourth preparation	—	—
		—	—
N	An overall summary and assessment of the application - always required	—	—

Part 3 Evaluation Form 3 -

for use in checking that all test and study reports required in accordance with Annex IIA have been provided

Active substance:

Applicant:

Date:

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N#	Justification provided L/N#	Undertaking provided Date/N#	Official use only * Data Gap Y/N#
1.1	Applicant (name, address, contact, telephone and telefax numbers) - always required	—	—	—	—
1.2	Manufacturer(s) (name, address, contact, telephone and telefax numbers) - always required	—	—	—	—
1.3	ISO common name proposed or accepted, and synonyms - always required	—	—	—	—
1.4	Chemical name as in Annex I to Directive 67/548/EEC, if not included in that Annex, in accordance with IUPAC and CA nomenclature - always required	—	—	—	—
1.5	Manufacturer's code number(s), for the active substance and formulations, materials concerned, countries in which used and periods for which used - always required	—	—	—	—
1.6	Existing CAS, CIPAC, EINECS and ELINCS numbers - always required	—	—	—	—
1.7	Molecular formula, molecular mass and structural formula - always required	—	—	—	—
1.8	Method of manufacture (pathways, by-products and impurities) for each plant, whether or not relevant to a pilot plant - always required	—	—	—	—

* To be completed by the Competent Authority of the Member State to which application is made

\# Y = yes; P = in part; N = no; L = location (volume and page) where justification can be found; Date = date report to be submitted

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
1.9	Minimum content (g/kg) of pure active substance (excluding inactive isomers), whether or not relevant to a pilot plant - always required	—		—	—
1.10	Inactive isomers[17] -				
	* IUPAC and CA names	—	—	—	—
	* ISO common name proposed or accepted	—	—	—	—
	* CAS, CIPAC, EINECS and ELINCS numbers	—	—	—	—
	* Molecular and structural formula	—	—	—	—
	* Molecular mass	—	—	—	—
	* Ratio of the content of isomers/diastereo-isomers	—	—	—	—
	* Maximum content in g/kg	—	—	—	—
	* Whether or not relevant to a pilot plant	—	—	—	—
	- required for all inactive isomers				

[17] To be completed for each individual inactive isomer, impurity and additive

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Impurities and additives [17] -				
	* IUPAC and CA names	—	—	—	—
	* ISO common name proposed or accepted	—	—	—	—
	* CAS, CIPAC, EINECS and ELINCS numbers	—	—	—	—
	* Molecular and structural formula	—	—	—	—
	* Molecular mass	—	—	—	—
	* Maximum content in g/kg	—	—	—	—
	* Whether or not relevant to a pilot plant	—	—	—	—
	* In the case of additives, their# function and trade names	—	—	—	—
	* In the case of impurities and by-products of particular environmental concern, details of the analytical methods	—	—	—	—
	- required for all impurities and by-products of particular toxicological and environmental concern - required for other components present in quantities > 1 g/kg				
1.11	Analytical profile of batches - always required	—	—	—	—
	Results of analyses of batches produced in laboratory or pilot scale production systems and used in toxicological testing - required where available and relevant	—	—	—	—
2.1.1	Melting point, freezing point or solidification point of purified active substance - always required	—	—	—	—
2.1.2	Boiling Point of purified active substance - required for liquid and low melting substances	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.1.3	Temperature at which decomposition or sublimation occurs - required where melting and/or boiling point cannot be determined because of decomposition or sublimation	—	—	—	—
2.2	Relative density of purified active substance - required for active substances which are liquids or solids	—	—	—	—
2.3.1	Vapour pressure of purified active substance - always required	—	—	—	—
2.3.2	Henry's law constant - required for solids and liquids	—	—	—	—
2.4.1	Description of the physical state and colour of both the purified active substance and active substance as manufactured - always required	—	—	—	—
2.4.2	Description of the odour of the purified active substance and active substance as manufactured - always required	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.5.1	Spectra, a table of signal characteristics and molecular extinction at relevant wavelengths for purified active substance				
	* Ultraviolet/visible (UV/VIS)	—	—	—	—
	* Infrared (R)	—	—	—	—
	* Nuclear magnetic resonance (NMR)	—	—	—	—
	* Mass spectra (MS)	—	—	—	—
	- always required				
	Wavelengths at which UV/VIS molecular extinction occurs, where appropriate, to include a wavelength at the highest absorption value above 290 nm - always required	—	—	—	—
	Optical purity - required for active substances which are resolved optical isomers	—	—	—	—
2.5.2	Spectra for impurities				
	* Ultraviolet/visible (UV/VIS)	—	—	—	—
	* Infrared (R)	—	—	—	—
	* Nuclear magnetic resonance (NMR)	—	—	—	—
	* Mass spectra (MS)	—	—	—	—
	- required for impurities of toxicological or environmental concern				
2.6	Solubility of purified active substance in water determined in the neutral range - required for compounds which do not form ions	—	—	—	—
	Solubility of purified active substance in water determined in the acidic range (pH 4 to 6) and in the alkaline range (pH 8 to 10) - required for compounds which form ions	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.7	Solubility in organic solvents at 15 to 25° C - always required	—	—	—	—
2.8	n-octanol/water partition coefficient - always required	—	—	—	—
	Effect of pH (4 to 10) on the n-octanol/water partition coefficient - required for acids of pKa value < 2, and bases of pKa value > 2	—	—	—	—
2.9.1	Hydrolysis rate of purified active substance at pH values 4, 7 and 9 under sterile conditions, in the absence of light				
	Identity of hydrolysis products - always required	—	—	—	—
	Rate constant observed - always required	—	—	—	—
	Estimated DT_{50} value - always required	—	—	—	—
2.9.2	Direct phototransformation of purified active substance in water using artificial light (simulating sunlight and excluding wavelengths $\lambda < 290$ nm) under sterile conditions, to include				
	* Photochemical halflife	—	—	—	—
	* Mass balance to account for 90 % of the applied radioactivity	—	—	—	—
	- required for compounds with a molar (decadic) absorption coefficient (ε) > 10 (1 x mol^{-1} x cm^{-1})				
	Identity of breakdown products - required for compounds which at any time during the study are present in quantities > 10 % of the active substance added	—	—	—	—

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 3** **Evaluation Form 3 Annex IIA Test and Study Reports**

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.9.3	* Quantum yield of direct phototransformation	—	—	—	—
	* Calculated theoretical lifetime in the top layer of aqueous systems and the real lifetime of the active substance	—	—	—	—
	- required where necessary to investigate direct phototransformation				
2.9.4	Dissociation in water of purified active substance				
	* Dissociation constant(s) (pKa values)	—	—	—	—
	* Identity of dissociated species formed	—	—	—	—
	- required where dissociation in water occurs				
	* Dissociation constant(s) (pKa values) of the active principle - required for active substances that are salts	—	—	—	—
2.10	Estimated photochemical oxidative degradation - always required	—	—	—	—
2.11.1	Flammability of the active substance as manufactured - required for compounds which are solids, gases or which evolve highly flammable gases	—	—	—	—
2.11.2	Auto-flammability of the active substance as manufactured - required for gases, liquids and solids which are not explosive or which do not ignite spontaneously in contact with air at ambient temperature	—	—	—	—
2.12	Flash point of the active substance as manufactured - required for compounds with a melting point below 40° C	—	—	—	—

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 3** **Evaluation Form 3 Annex IIA Test and Study Reports**

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.13	Explosive properties of the active substance as manufactured - required for liquids, pastes and solids	—	—	—	—
2.14	Surface tension of the active substance as manufactured - always required	—	—	—	—
2.15	Oxidizing properties of the active substance as manufactured - required except where examination of its structural formula establishes beyond reasonable doubt that the active substance is incapable of reacting exothermically with a combustible material	—	—	—	—
3.1	Function *e.g.* fungicide - always required	—		—	—
3.2.1	Nature of the effects on harmful organisms *e.g.* contact action - always required	—		—	—
3.2.2	Whether or not translocated in plants and if translocated whether such translocation is apoplastic, symplastic or both - always required	—		—	—
3.3	Fields of use *e.g.* forestry - always required	—		—	—
3.4.1	Details of existing and intended uses (crops, groups of crops, plants or plant products treated or protected) - always required	—		—	—
3.4.2	Details of harmful organisms against which protection is afforded - required where relevant	—		—	—
3.4.3	Effects achieved *e.g.* sprout suppression - required where relevant	—		—	—

Active Substance: Applicant: Date:

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
3.5.1	Statement of the mode of action of the active substance in terms of biochemical and physiological mechanism(s) and biochemical pathway(s) involved - required where and to the extent that it has been elucidated	—		—	—
3.5.2	Details of active metabolites and degradation products, cross referenced to the information provided under points 5.1, 5.8, 5.10, 6.1, 6.3, 6.5, 6.9, 7.1, 7.2 and 9, to include				
	* IUPAC and CA names	—		—	—
	* ISO common name proposed or accepted	—		—	—
	* CAS, CIPAC, EINECS and ELINCS numbers	—		—	—
	* Molecular and structural formula	—		—	—
	* Molecular mass	—		—	—
	- required where the active substance must be converted to a metabolite or degradation product following application or use of preparations containing it, to exert its intended effect				
3.5.3	Information relative to the formation of active metabolites and degradation products, to include				
	* The processes, mechanisms and reactions involved	—		—	—
	* Kinetic and other data concerning the rate of conversion and if known the rate limiting step	—		—	—
	* Environmental and other factors effecting the rate and extent of conversion	—		—	—
	- required where relevant and available				

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 3** **Evaluation Form 3 Annex IIA Test and Study Reports**

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
3.6	Information on the possible occurrence of the development of resistance or cross-resistance - required where it is available	—		—	—
3.7	A safety data sheet pursuant to Article 27 of Council Directive 67/548/EEC - always required	—		—	—
3.8.1	Pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis - required for active substances with a halogen content greater than 60 %	—	—	—	—
	Detailed instructions for safe disposal - always required	—	—	—	—
3.8.2	Methods other than controlled incineration for disposal of the active substance, contaminated packaging and contaminated materials -				
	* Detailed description of such methods	—	—	—	—
	* Data to establish their effectiveness and safety	—	—	—	—
	- required where available				
3.9	Procedures for the decontamination of water in the case of an accident - always required	—		—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4	* Analytical standards for pure active substance - required where requested	—		—	—
	* Samples of the active substance as manufactured - required where requested	—		—	—
	* Analytical standards for relevant metabolites and other components included in the residue definition - required where requested	—	—	—	—
	* Samples of reference substances for relevant impurities - if available, required where requested	—	—	—	—
4.1.1	Description of analytical methods for the analysis of the active substance as manufactured - always required	—		—	—
	Applicability of existing CIPAC methods - always required	—	—	—	—
4.1.2	Description of analytical methods for the determination of impurities (non-active components arising from the manufacturing process or from degradation during storage) which are of toxicological, ecotoxicological or environmental concern or which are present in quantities ≥ 1g/kg in the active substance as manufactured - always required	—	—	—	—
	Description of analytical methods for the determination of additives (*e.g.* stabilizers) in the active substance as manufactured - always required	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.1.3.1	For each method submitted (active substance and impurities) -				
	* Specificity	—	—	—	—
	* Extent of interference by other substances present	—	—	—	—
	* Explantation of interferences which contribute more than ± 3 % of the total quantity determined	—	—	—	—
	- always required				
4.1.3.2	For each method submitted, linearity over an appropriate range -				
	* Equation of the calibration line	—	—	—	—
	* Correlation co-efficient	—	—	—	—
	* Representative labelled documentation *e.g.* chromatograms	—	—	—	—
	- always required				
4.1.3.3	For each method submitted, accuracy -				
	* Pure active substance - always required	—	—	—	—
	* Impurities - required for impurities of toxicological, ecotoxicological or environmental concern present in amounts ≥ 1g/kg in the active substance as manufactured	—	—	—	—

Active Substance: Applicant: Date:

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.1.3.4	For each method submitted, repeatability (at least 5 determinations) -				
	* % relative standard deviation (RSD) - always required	—	—	—	—
	* Indication as to whether outliers identified have been discarded - always required	—	—	—	—
	* reasons for the occurrence of outliers - must be attempted where outliers are discarded	—	—	—	—
4.2.1	Description of analytical methods for the determination of residues (all components included in the residue definition proposed (see point 6) to enable compliance with MRLs to be determined or to determine dislogeable residues - always required	—	—	—	—
	For each method and representative matrix -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Validation - independent laboratory	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.2.2	Description of methods for analysis of soil for parent compound and metabolites of toxicological, ecotoxicological or environmental concern - always required	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				
4.2.3	Description of methods for analysis of water (drinking water, ground water and surface water) for parent compound and metabolites of toxicological, ecotoxicological or environmental concern - always required	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.2.4	Description of methods for analysis of air for active substance and metabolites, formed during or shortly after application, of toxicological concern - required unless operator exposure, worker exposure or bystander exposure are unlikely to occur	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				
4.2.5	Analytical methods for parent compound and toxicologically, ecotoxicologically or environmentally significant metabolites in body fluids and tissues - required for active substances classified as *Toxic* or *Very Toxic*	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if necessary)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 3** **Evaluation Form 3 Annex IIA Test and Study Reports**

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.1	Toxicokinetic studies -				
	* Single dose, oral route, in rats	—	—	—	—
	* Second single dose, oral route, in rats	—	—	—	—
	* Repeated dose, oral route, in rats	—	—	—	—
	- always required				
5.2.1	Acute oral toxicity - always required	—	—	—	—
5.2.2	Acute percutaneous toxicity - always required	—	—	—	—
5.2.3	Acute inhalation toxicity - required where the active substance is . a gas or liquified gas, . is to be used as a fumigant, . is to be included in a smoke generating aerosol or vapour releasing preparation, . is to be used with fogging equipment, . has a vapour pressure > 1 x 10^{-2} Pa and is to be included in preparations to be used in enclosed spaces such as warehouses or glasshouses, . is to be included in preparations which are powders containing a significant proportion of particles of diameter < 50 μm (> 1 % on a weight basis), or . is to be included in preparations to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 μm (> 1 % on a weight basis)	—	—	—	—
5.2.4	Skin irritation - required except where severe skin effects may be produced or effects can be excluded (see EEC Method B4)	—	—	—	—
5.2.5	Eye Irritation - required except where severe effects may be produced (see EEC Method B5)	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.2.6	Skin sensitization - required except where the active substance is a known sensitizer	—	—	—	—
5.3.1	Oral 28-day toxicity - where conducted, must be submitted	—	—	—	—
5.3.2	Oral 90-day toxicity (rat) - always required	—	—	—	—
	Oral 90-day toxicity (dog) - always required	—	—	—	—
	Oral 1 year toxicity (dog) - required where in 90-day studies, the dog is more sensitive than the rat, where such data are likely to be of value in extrapolating results obtained to man	—	—	—	—
5.3.3	28-day inhalation toxicity (rat) - for volatile substances (vapour pressure > 10^{-2} Pa), expert judgement required to determine whether testing by the oral or inhalation is required	—	—	—	—
	90-day inhalation toxicity (rat) - for volatile substances (vapour pressure > 10^{-2} Pa), expert judgement required to determine whether testing by the oral or inhalation is required	—	—	—	—
	Percutaneous 28-day toxicity (rat) - required where operator exposure by the percutaneous route is significant, except where a 90-day percutaneous study is conducted	—	—	—	—
	Percutaneous 90-day toxicity (rat) - required where operator exposure by the percutaneous route is significant except where the results of percutaneous 28-day toxicity testing indicate low toxicity by the percutaneous route	—	—	—	—

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.5	Long-term (2 years) oral toxicity in the rat (can be a combined long-term and carcinogenicity study) - required unless it is shown that exposure does not occur, *viz* toxicokinetic data demonstrates that absorption from the gut, through the skin or *via* the pulmonary system does not occur	—	—	—	—
	Carcinogenicity study in the rat (can be a combined long-term and carcinogenicity study) - required unless it is shown that exposure does not occur, *viz* toxicokinetic data demonstrates that absorption from the gut, through the skin or *via* the pulmonary system does not occur	—	—	—	—
	Carcinogenicity study in the mouse - required unless it is shown that exposure does not occur, *viz* toxicokinetic data demonstrates that absorption from the gut, through the skin or *via* the pulmonary system does not occur	—	—	—	—
	Mechanism of action and supporting data - required where a non-genotoxic mechanism for carcinogenicity is suggested	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.6.1	Two generation reproductive toxicity in the rat - always required	—	—	—	—
	Supplementary studies -				
	* Separate male and female studies	—	—	—	—
	* Three segment designs	—	—	—	—
	* Dominant lethal assay for male fertility	—	—	—	—
	* Cross-matings of treated males with untreated females and *vice versa*	—	—	—	—
	* Effect on spermatogenesis	—	—	—	—
	* Effects on oogenesis	—	—	—	—
	* Sperm motility, mobility and morphology	—	—	—	—
	* Investigation of hormonal activity	—	—	—	—
	- required where necessary for a better interpretation of effects on reproduction				
5.6.2	Teratogenicity test by the oral route in the rat - always required	—	—	—	—
	Teratogenicity test by the oral route in the rabbit - always required	—	—	—	—
5.7	Delayed neurotoxicity following acute exposure - required for substances of similar or related structures to those capable of inducing delayed neurotoxicity such as organophosphates	—	—	—	—
5.8.1	Toxicity studies on metabolites - required where as a result of metabolism in plants or as a result of processing, metabolites not formed in animals occur, unless it is shown that a health risk does not arise for consumers or workers	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.8.2	Supplementary studies - required in particular cases, depending on the results of the available toxicological and metabolism studies and the most important exposure routes	—	—	—	—
5.9.1	Report on medical surveillance on manufacturing plant personnel - always required	—		—	—
5.9.2	Report on clinical cases and poisoning incidents - always required	—		—	—
5.9.3	Observations on exposure of the general population and epidemiological studies - required where available	—		—	—
5.9.4	Clinical signs and symptoms of poisoning and details of clinical tests - always required	—		—	—
5.9.5	First aid measures - always required	—		—	—
	Therapeutic regimes - always required	—		—	—
5.9.6	Expected effects and duration of poisoning as a function of the type, level and duration of exposure or ingestion - always required	—		—	—
	Expected effects and duration of poisoning as a function of varying time periods between exposure or ingestion and commencement of treatment - always required	—		—	—
5.10	Summary of mammalian toxicity and overall evaluation - always required	—		—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
6	Stability of residues during storage of samples - required for . compounds known to be volatile or labile . samples not frozen within 24 hours of sampling or not analyzed within 30 days of sampling or in the case of radiolabelled material, not analyzed within 6 months of sampling	—	—	—	—
	Stability of residues in sample extracts - required where samples are not analyzed within 24 hours of extraction	—	—	—	—
6.1	Metabolism, distribution and expression of residues in plants, in at least three crops representative of the different categories of crop (root vegetables; leafy crops; fruits; pulses and oilseed; cereals) - required unless residues do not remain on plants or plant products used as food or feed	—	—	—	—
6.2	Metabolism, distribution and expression of residues in livestock -				
	* Poultry or lactating ruminants (goat or cow) - required where there are significant residues in feed (≥ 0.1 mg/kg of the total diet as received) except in special cases (*e.g.* accumulation of active substance)	—	—	—	—
	* Pigs - required where metabolic patterns in ruminants differ significantly from those in the rat	—	—	—	—

Active Substance: Applicant: Date:

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
6.3	Residue trials (supervised field trials) for crops or plant products used as food or feed on which use is proposed or where residues from soil can be taken up				
	* Pre-harvest use on major crops - trials over two seasons are required; if use is proposed in both regions, at least 8 trials representative of the northern European region and a further 8 trials representative of the Mediterranean region, are required, unless it can be justified that there are no residues in the edible part of the plant, or unless extrapolation from adequate data on another crop is possible; the number of trials can be reduced where it can be justified that the residue levels in plants and plant products are lower than the LOQ; where a significant part of the consumable crop is present at time of application, residue disappearance curves for half of the trials are required	—	—	—	—
	* Pre-harvest use on minor crops - trials over two seasons are required; if use is proposed in both regions, at least 4 trials representative of the northern European region and a further 4 trials representative of the Mediterranean region, are required, unless it can be justified that there are no residues in the edible part of the plant, or unless extrapolation from adequate data on another crop is possible; the number of trials can be reduced where it can be justified that the residue levels in plants and plant products are lower than the LOQ; where a significant part of the consumable crop is present at time of application, residue disappearance curves for half of the trials are required	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Post-harvest uses - at least 4 trials carried out at different locations in one growing season and with different cultivars are required for each application method and store type, unless extrapolation from adequate data on another stored crop is possible	—	—	—	—
6.4	Livestock feeding studies -				
	* Poultry and/or lactating ruminants (goat or cow) - required . where significant residues occur in crops or part of the crop fed to animals (≥ 0.1 mg/kg of the total diet as received) except in special cases (*e.g.* accumulation of active substance), and . on the basis of the metabolism studies it is evident that significant residues (≥ 0.01 mg/kg or greater than the LOQ if that is > 0.01 mg/kg) occur in any edible animal tissue, taking into account the residue levels in potential feedingstuffs performed at the 1x dose rate	—	—	—	—
	* Pigs - required where metabolic patterns in ruminants differ significantly from those in the rat, unless the expected intake by pigs is not significant	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
6.5.1	Effects of industrial processing and/or household preparation (representative processing situations) on the nature of the residue - required unless . the plant or plant product is mostly eaten raw (except products with inedible portions such as citrus, banana or kiwi fruit), . the total TMDI is less than 10 % of the ADI, . no significant residues (> 0.1 mg/kg) occur in the plant or plant product to be processed, or . no analytically determinable residues occur in the plant or plant product processed				
	- required for determinable residues below 0.1 mg/kg where the active substance has high acute toxicity or a low ADI	—	—	—	—
	Distribution of the residue in peel/pulp - may be required for plant products with inedible portions such as citrus, banana or kiwi fruit	—	—	—	—
6.5.2	Effects of industrial processing and/or household preparation on residue levels				
	* Balance studies on a core set of representative processes - required unless . the plant or plant product is mostly eaten raw (except products with inedible portions such as citrus, banana or kiwi fruit), . the total TMDI is less than 10 % of the ADI, . no significant residues (> 0.1 mg/kg) occur in the plant or plant product to be processed, or . no analytically determinable residues occur in the plant or plant product processed				
	- required for determinable residues below 0.1 mg/kg where the active substance has high acute toxicity or a low ADI	—	—	—	—
	* Follow-up studies to determine concentration or dilution factors - required where the processed product is an important part of the diet and if a significant transfer of residue into the processed products could occur	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
6.6	Residues in succeeding crops				
	* Theoretical consideration of the nature and level of the residue- residue required where data generated in accordance with point 7.1, or generated in accordance with Annex IIIA, point 9.1, show that significant residues (> 10% of the applied active substance as a total of unchanged active substance and its relevant metabolites or degradation product) remain in soil or in plant materials (*e.g.* straw or organic material) up to sowing or planting time of succeeding crops and which could lead to residues above the LOQ at harvest	—	—	—	—
	* Metabolism and distribution studies on representative crops - required if the likelihood of residues in succeeding crops can not be excluded	—	—	—	—
	* Field trials on representative crops - required where necessary	—	—	—	—
6.7	Proposed residue definition - always required	—		—	—
	Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed, including details of statistical analyses used - always required	—		—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
6.8	Proposed pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces and a justification for each proposal				
	* Pre-harvest interval (in days) for each relevant crop	—	—	—	—
	* Re-entry period (in days) for livestock, to areas to be grazed	—	—	—	—
	* Re-entry period (in hours or days) for man to crops, buildings or spaces treated	—	—	—	—
	* Withholding period (in days) for animal feedingstuffs	—	—	—	—
	* Waiting period (in days) between last application and sowing or planting the crop to be protected	—	—	—	—
	* Waiting period (in days) between application and handling treated products	—	—	—	—
	* Waiting period (in days) between last application and sowing or planting succeeding crops	—	—	—	—
	- required where risks to man or livestock may arise				
6.9	Estimation of the potential and actual exposure through diet and other means -				
	* TMDI calculations - always required	—		—	—
	* NEDI calculations - required unless the TMDI calculations demonstrate that the ADI will not be exceeded	—		—	—
6.10	Summary and evaluation of residue behaviour - always required	—		—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.1.1.1.1	Aerobic degradation in (one) soil - required except where the manner of use of preparations containing the active substance precludes soil contamination	—	—	—	—
7.1.1.1.2	Supplementary soil degradation studies -				
	* Anaerobic degradation - required if exposure to anaerobic conditions is likely following use of preparations containing the active substance	—	—	—	—
	* Soil photolysis - required where deposition of the active substance at the soil surface is likely	—	—	—	—
7.1.1.2.1	Rate of degradation in soil - laboratory studies				
	* Aerobic degradation of the active substance at 20 °C in 3 soils (additional to the soil used in the study at 7.1.1.1.1) - required except where the manner of use of preparations containing the active substance precludes soil contamination	—	—	—	—
	* Aerobic degradation of the active substance at 10 °C in 1 of the soils used to investigate degradation at 20 °C - required to investigate the Influence of temperature on degradation, except where the manner of use of preparations containing the active substance precludes soil contamination (until a validated Community validation model becomes available)	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Aerobic degradation of relevant metabolites, degradation and reaction products in 3 soils (additional to the soil used in the study at 7.1.1.1.1) - required for compounds which at any time during the studies account for more than 10 % of the active substance added except where their DT_{50} values were determined from the results of studies with the active substance	—	—	—	—
	* Anaerobic degradation in the soil used in the study reported under point 7.1.1.1.2 - required if exposure to anaerobic conditions is likely following use of preparations containing the active substance	—	—	—	—
	* Anaerobic degradation of relevant metabolites, degradation and reaction products in the soil used in the study reported under point 7.1.1.1.2 - required for compounds which at any time during the studies account for more than 10 % of the active substance added except where their DT_{50} values were determined from the results of studies with the active substance	—	—	—	—
7.1.1.2.2	Rate of degradation in soil - field studies				
	Soil dissipation testing in a range of representative soils - normally 4 soils	—	—	—	—
	- required where DT_{50Lab} determined at 20° C and a soil moisture content equivalent to a pF value of 2 - 2.5 > 60 days - where use is envisaged in cold climates, required where DT_{50Lab} > determined at 10° C and a soil moisture content equivalent to a pF value of 2 - 2.5 > 90 days				

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Soil residue testing - required where DT_{50Lab} is greater than one third of the period between application and harvest and where absorption by the succeeding crop is possible, unless - . soil residues at sowing or planting of a succeeding crop can be reliably estimated from the data on soil dissipation, or . it can be shown that the residues concerned will not be phytotoxic to or leave unacceptable residues in rotational crops	—	—	—	—
	Soil accumulation testing on 2 relevant soils - required where on the basis of soil dissipation studies, $DT_{90f} > 1$ year and repeated application in the same or succeeding years is intended, unless reliable information is provided using a model calculation or another appropriate assessment	—	—	—	—
7.1.2	Adsorption and desorption of the active substance in four soils - required except where the manner of use of preparations containing the active substance precludes soil contamination	—	—	—	—
	Adsorption and desorption of all relevant metabolites, degradation and reaction products in 3 soils - required for compounds which at any time during the soil degradation studies account for more than 10 % of the active substance added	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.1.3.1	Column leaching studies with the active substance using 4 soils - required where in the adsorption and desorption studies reliable adsorption coefficient values were not obtained	—	—	—	—
	Column leaching studies with relevant metabolites, degradation and reaction products using 4 soils - required where testing is possible for compounds which at any time during the soil degradation or soil dissipation studies account for more than 10 % of the active substance added, where in the adsorption and desorption studies reliable adsorption coefficient values were not obtained	—	—	—	—
7.1.3.2	Aged residue column leaching - required except where - . the manner of use of preparations containing the active substance precludes soil contamination, or . separate studies for the metabolites, degradation or reaction products were performed in accordance with points 7.1.2 or 7.1.3.1	—	—	—	—
7.1.3.3	Lysimeter studies - expert judgement required to decide if lysimeter or field leaching studies are required	—	—	—	—
	Field leaching studies - expert judgement required to decide if field leaching or lysimeter studies are required	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.2.1.1	Hydrolysis rate of relevant metabolites, degradation and reaction products at pH values 4, 7 and 9 under sterile conditions, in the absence of light				
	* Identity of hydrolysis products	—	—	—	—
	* Rate constant observed	—	—	—	—
	* Estimated DT_{50} value	—	—	—	—
	- required for compounds which at any time account for more than 10 % of the active substance, unless sufficient information on their degradation is available from testing on the active substance (point 2.9.1)				
7.2.1.2	Direct phototransformation of relevant metabolites, degradation and reaction products in water using artificial light (simulating sunlight and excluding wavelengths $\lambda < 290$ nm) under sterile conditions, to include				
	* Photochemical halflife	—	—	—	—
	* Mass balance to account for 90 % of the applied radioactivity - unless sufficient information on their degradation is available from testing on the active substance (point 2.9.2 and 2.9.3	—	—	—	—
	- required for compounds which at any time account for more than 10 % of the active substance, and have a molar (decadic) absorption coefficient (ε) > 10 (1 x mol^{-1} x cm^{-1}),				
	* Identity of breakdown products - required for compounds which at any time during the study are present in quantities > 10 % of the substance added	—	—	—	—

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Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Quantum yield of direct phototransformation	—	—	—	—
	* Calculated theoretical lifetime in the top layer of aqueous systems and the real lifetime of the substance added	—	—	—	—
	- required where necessary to investigate direct phototransformation				
7.2.1.3.1	Ready biodegradability of the active substance - required where conducted pursuant to the provisions of Directive 67/548/EEC	—	—	—	—
7.2.1.3.2	Water/sediment study - required unless it is justified that contamination of surface water will not occur	—	—	—	—
7.2.1.4	Degradation in the saturated zone of active substance, metabolites, degradation and reaction products - expert judgement required to determine when necessary	—	—	—	—
7.2.2	Rate and route of degradation in air (as far as not covered by point 2.10) - no requirements currently specified				
7.3	Definition of the residue - always required	—		—	—
7.4	Monitoring data concerning fate and behaviour of the active substance and of relevant metabolites, degradation and reaction products - available data must be reported	—	—	—	—

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 3** **Evaluation Form 3 Annex IIA Test and Study Reports**

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.1.1	Acute oral toxicity to a quail species (Japanese or Bobwhite), or to mallard duck - required unless use is intended solely in enclosed spaces	—	—	—	—
8.1.2	Avian dietary toxicity (5-day) test in a quail species or in mallard duck - required unless use is intended solely in enclosed spaces or testing in accordance with point 8.1.3 is reported	—	—	—	—
	Avian dietary toxicity (5-day) test in a second unrelated species - required where the acute oral NOEL is ≤ 500 mg/kg body weight or the 5-day NOEC < 500 mg/kg food	—	—	—	—
8.1.3	Subchronic and reproductive toxicity to birds - required unless it is justified that continued or repeated exposure of adults or of nest sites during the breeding season is unlikely to occur	—	—	—	—
8.2.1	Acute toxicity of the active substance to fish -				
	* Rainbow trout (*Oncorhynchus mykiss*)	—	—	—	—
	* Warm water fish species	—	—	—	—
	- always required				
	Acute toxicity of metabolites, degradation or reaction products to the more sensitive of the fish species used to test the acute toxicity of the active substance - required where such compounds constitute a relevant risk to fish and their effects are not covered by the tests using the active substance	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.2.2.1	Chronic toxicity (28 day exposure) to juvenile fish - growth and behaviour - expert judgement necessary to decide if testing is required	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.2.2.2	Fish early life stage toxicity test - expert judgement necessary to decide if testing is required	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.2.2.3	Fish life cycle test - expert judgement necessary to decide if testing is required	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.2.3	Bioconcentration potential of the active substance in fish - required where the n-octanol/water partition coefficient log P_{ow} ≥ 3, unless it is justified that prolonged or repeated exposure is unlikely to occur	—	—	—	—
	Bioconcentration potential of metabolites, degradation and reaction products - required where the n-octanol/water partition coefficient log P_{ow} ≥ 3, unless it is justified that prolonged exposure is unlikely to occur	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.2.4	Acute toxicity to aquatic invertebrates -				
	Acute toxicity (24 and 48 hour) for *Daphnia* preferably (*Daphnia magna*) - always required	—	—	—	—
	Acute toxicity (24 and 48 hour) for at least one representative species from each of the following groups -				
	* Aquatic insects	—	—	—	—
	* Aquatic crustaceans (species unrelated to *Daphnia*)	—	—	—	—
	* Aquatic gastropod molluscs	—	—	—	—
	- required where preparations containing the active substance are to be used directly on surface water				
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.2.5	Chronic toxicity to aquatic invertebrates -				
	Chronic toxicity in *Daphnia magna* (21-day) - required unless it is justified that continued or repeated exposure is unlikely to occur	—	—	—	—
	Chronic toxicity for at least one representative species from each of the following groups -				
	* Aquatic insects	—	—	—	—
	* Aquatic gastropod molluscs	—	—	—	—
	- required unless it is justified that continued or repeated exposure is unlikely to occur				
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.2.6	Effects on algal growth and growth rate - always required	—	—	—	—
	Effects on algal growth and growth rate in a second species - required for herbicides	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.2.7	Effects on sediment dwelling organisms				
	* Acute test	—	—	—	—
	* Chronic test	—	—	—	—
	- required where the active substance is likely to partition to and persist in aquatic sediments - expert judgement necessary to determine whether acute or chronic testing is required				
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.2.8	Effects on aquatic plants - required for herbicides	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
8.3.1.1	Acute toxicity to bees -				
	* Acute oral toxicity	—	—	—	—
	* Acute contact toxicity	—	—	—	—
	- required except where preparations containing the active substance are for exclusive use in situations where bees are not exposed . food storage in enclosed spaces . non-systemic seed dressings . non-systemic preparations for application to soil . non-systemic dipping treatments for transplanted crops and bulbs . wound sealing and healing treatments . rodenticidal baits . use in glasshouses without pollinators				
8.3.1.2	Bee brood feeding test - required for active substances which may act as an insect growth regulator, unless it can be justified that exposure is unlikely	—	—	—	—

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.3.2	Effects on non-target terrestrial arthropods using artificial substrates				
	* Parasitoid (*e.g. Aphidius rhopalosiphi*)	—	—	—	—
	* Predatory mites (*e.g. Typhlodromus pyri*)	—	—	—	—
	* Ground dwelling predatory species (selected to be relevant to the intended uses of preparations)	—	—	—	—
	* Foliage dwelling predatory species (selected to be relevant to the intended uses of preparations)	—	—	—	—
	- required unless adverse effects can be clearly predicted from other studies, except where preparations containing the active substance are for exclusive use in situations where exposure does not occur . food storage in enclosed spaces . wound sealing and healing treatments . rodenticidal baits				
	Effects on non-target terrestrial arthropods in extended laboratory/semi field tests				
	* Parasitoid (*e.g. Aphidius rhopalosiphi*)	—	—	—	—
	* Predatory mites (*e.g. Typhlodromus pyri*)	—	—	—	—
	* Ground dwelling predatory species (selected to be relevant to the intended uses of preparations)	—	—	—	—
	* Foliage dwelling predatory species (selected to be relevant to the intended uses of preparations)	—	—	—	—
	- required for species relevant to proposed uses of preparations, where effects are observed in testing with artificial substrates, or where adverse effects were predicted from other studies and testing using artificial substrates was not carried out				

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.4.1	Acute toxicity to earthworms - required where preparations containing the active substance are to be applied to soil or can contaminate soil under practical conditions of use	—	—	—	—
8.4.2	Sublethal effects on earthworms - expert judgement is necessary to determine if testing is required	—	—	—	—
8.5	Impact on soil microbial activity				
	* Nitrogen transformation	—	—	—	—
	* Carbon mineralization	—	—	—	—
	- required where preparations containing the active substance are to be applied to soil or can contaminate soil under practical conditions of use				
	Rates of recovery following treatment - required for soil sterilants	—	—	—	—
8.6	Summary of all available data from preliminary tests used to assess biological activity and dose range finding, which may provide information on other non-target species (flora and fauna) - required where available	—	—	—	—
	A critical assessment as to the relevance of the preliminary test data to potential impact on non-target species - required where preliminary test data is available	—	—	—	—
8.7	Effects on biological methods for sewage treatment - required where adverse effects on sewage treatment plants can occur	—	—	—	—

Active Substance: **Applicant:** **Date:**

Annex IIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
9	Summary and evaluation of points 7 and 8 - always required	—		—	—
10	Justified proposals for the classification and labelling of the active substance according to Directive 67/548/EEC				
	* Hazard symbol(s)	—		—	—
	* Indications of danger	—		—	—
	* Risk phrases	—		—	—
	* Safety phrases	—		—	—
	- always required				

Part 4 **Evaluation Form 4 -**

for use in checking that all test and study reports required in accordance with Annex IIIA have been provided

Preparation:

Active substance(s):

Applicant:

Date:

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N#	Justification provided L/N#	Undertaking provided Date/N#	Official use only * Data Gap Y/N#
1.1	Applicant (name, address, contact, telephone and telefax numbers) - always required	—	—		—
1.2	Manufacturer(s) of the preparation (name, address, contact, telephone and telefax numbers - always required	—	—		—
	Manufacturer of the active substance(s) (name, address, contact, telephone and telefax numbers - always required	—	—		—
	Statement of purity and detailed information on impurities - required where the active substance in the preparation is from a manufacturer other the manufacturer for which the Annex II dossier was submitted	—	—		—
1.3	Trade name or proposed trade name and manufacturers code number(s), for the preparation and similar preparations (differences to be specified) - always required	—	—		—

* To be completed by the Competent Authority of the Member State to which application is made

\# Y = yes; P = in part; N = no; L = location (volume and page) where justification can be found; Date = date report to be submitted

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
1.4.1	Content expressed: - for solids, aerosols, volatile liquids (maximum boiling point 50° C) or viscous liquids (lower limit 1 Pa at 20° C) as a percentage by weight; - for other liquids as a percentage by weight and in grams per litre at 20° C; - for gasses as a percentage by volume				
	* Technical active substance	—		—	—
	* Pure active substance	—		—	—
	* Formulants	—		—	—
	- always required				
1.4.2	ISO common name proposed or accepted for active the substances, and synonyms - always required	—		—	—
	Existing CIPAC, EINECS and ELINCS numbers for the active substance(s) - always required	—		—	—
	Salt, ester, anion or cation present for each active substance - required where relevant	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
1.4.3	For each formulant, or component in formulants				
	* Chemical name as in Annex I to Directive 67/548/EEC, if not included in that Annex, in accordance with IUPAC and CA nomenclature	—		—	—
	* Structure or structural formula	—		—	—
	* Existing CAS, CIPAC, EINECS and ELINCS numbers	—		—	—
	* Trade name	—		—	—
	- always required	—		—	—
	* Specification of the formulant - required where the information provided does not fully identify a formulant	—		—	—
1.4.4	Function of each formulant - always required	—		—	—
1.5	Type of preparation and code - always required	—		—	—
1.6	Function (herbicide, insecticide *etc*) - always required	—		—	—
2.1	Description of the physical state of the preparation and its colour and odour - always required	—		—	—
2.2.1	Explosive properties of the preparation - required except where available thermodynamic information establishes beyond reasonable doubt that the preparation is incapable of exothermic reaction	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.2.2	Oxidizing properties of the preparation - required except where it can be shown without reasonable doubt on the basis of thermodynamic information, that the preparation is incapable of reacting exothermically with combustible materials	—	—	—	—
2.3	The flash point of the preparation - required for liquids that contain flammable solvents	—	—	—	—
	The flammability of the preparation - required for solid preparations and gases	—	—	—	—
	The auto-flammability of the preparation - required for preparations which are gases, liquids and solids and which are not explosive	—	—	—	—
2.4.1	Acidity or alkalinity and pH value - required for preparations which are acidic (pH < 4) or alkaline (pH > 10)	—	—	—	—
2.4.2	pH of a 1 % aqueous dilution, emulsion or dispersion, as appropriate - required for preparations applied as an aqueous dilution	—	—	—	—
2.5.1	Kinematic viscosity of the preparation - required for preparations for ultra low volume (ULV) use	—	—	—	—
2.5.2	Viscosity of the preparation and details of the test conditions - required for non newtonian liquids	—	—	—	—
2.5.3	Surface tension of the preparation - required for liquids	—	—	—	—
2.6.1	Relative density of the preparation - required for liquids	—	—	—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.6.2	Bulk or tap density of the preparation - required for powders and granules	—	—	—	—
2.7.1	Stability after storage for 14 days at 54° C - always required	—	—	—	—
	Stability after storage for other periods and/or temperatures (*e.g.* eight weeks at 40° C or 12 weeks at 35° C) - required if the preparation is heat sensitive	—	—	—	—
	Minimum content after heat stability testing - required where the active substance content decreased by more than 5 % in heat stability testing	—	—	—	—
2.7.2	Effect of low temperature on stability - required for liquid preparations	—	—	—	—
2.7.3	Shelf life following storage at ambient temperature - always required	—	—	—	—
	Shelf life in months - required where storage life is less than 2 years	—	—	—	—
2.8.1	Wettability - required for solid preparations which are diluted with water for use	—	—	—	—
2.8.2	Persistent foaming - required for preparations which are diluted with water for use	—	—	—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.8.3	Suspensibility - required for water dispersible products (*e.g.* wettable powders, water dispersible granules, suspension concentrates)	—	—	—	—
	Spontaneity of dispersion - required for water dispersible products (*e.g.* suspension concentrates)	—	—	—	—
2.8.4	Dilution stability - required for water soluble products	—	—	—	—
2.8.5	Dry sieve test - required for dustable powders	—	—	—	—
	Wet sieve test - required for water dispersible products	—	—	—	—
2.8.6.1	Size distribution of particles - required for powders	—	—	—	—
	Nominal size range of granules - required for granules for direct application and water dispersible granules	—	—	—	—
2.8.6.2	Dust content - required for granular preparations	—	—	—	—
	Particle size of dust - required for granular preparations where relevant to operator exposure (point 7.2.1)	—	—	—	—
2.8.6.3	Friability and attrition characteristics of granules - required when internationally agreed methods are available - available data, and details of the method used, always required	—	—	—	—

Preparation : **Active Substance:** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.8.7.1	**Emulsifiability** - required for preparations which form emulsions	—	—	—	—
	Emulsion stability - required for preparations which form emulsions	—	—	—	—
	Re-emulsifiability - required for preparations which form emulsions	—	—	—	—
2.8.7.2	**Stability of dilute emulsions** - required for preparations which form emulsions	—	—	—	—
	Stability of emulsions - required for preparations which are emulsions	—	—	—	—
2.8.8.1	**Flowability** - required for granular preparations	—	—	—	—
2.8.8.2	**Pourability (including rinsed residue)** - required for preparations which are suspensions (*e.g.* suspension concentrates, suspo-emulsions)	—	—	—	—
2.8.8.3	**Dustability following accelerated storage** - required for dustable powders	—	—	—	—
2.9.1	**Physical compatibility of tank mixes** - required for mixtures to be mentioned on product labels	—	—	—	—
2.9.2	**Chemical compatibility of tank mixes** - required for mixtures to be mentioned on product labels, except where examination of the individual properties of the preparations establishes beyond reasonable doubt that there is no possibility of reaction taking place	—	—	—	—
2.10	**Distribution** - required for preparations for seed treatment	—	—	—	—
	Adhesion - required for preparations for seed treatment	—	—	—	—

Preparation: Active Substance(s): Applicant: Date:

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
2.11	Summary and evaluation of points 2.1 to 2.10 - always required	—		—	—
3.1	Fields of use *e.g.* forestry - always required	—		—	—
3.2	Nature of the effects on harmful organisms *e.g.* contact action - always required	—		—	—
3.3	Details of existing and intended uses (crops, groups of crops, plants or plant products treated or protected) - always required	—		—	—
	Details of harmful organisms against which protection is afforded - required where relevant	—		—	—
	Effects achieved *e.g.* sprout suppression - required where relevant	—		—	—
3.4	Rate of application per unit (ha, m^2, m^3, tonne) treated, in terms of g or kg of preparation and active substance - required for each use and method of application	—		—	—
3.5	Concentration of active substance in material used (*e.g.* diluted spray, baits, treated seed) in g/l, g/kg, mg/kg or g/tonne - always required	—		—	—
3.6	Description of the method of application, type of equipment used and type and volume of diluent per unit of area or volume - always required	—		—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
3.7	Maximum number of applications and their timing - always required	—		—	—
	For each application, growth stages of the crop or plants to be protected - required where timing of applications is important	—		—	—
	For each application, development stages of the harmful organism concerned - required where timing of applications is important	—		—	—
	Duration of protection afforded by each application - required where more than one application is recommended	—		—	—
	Duration of protection afforded by the maximum number of applications - required where more than one application is recommended	—		—	—
3.8	Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops - required where phytotoxic effects on succeeding crops may arise	—		—	—
	Limitations on choice of succeeding crops, if any - always required	—		—	—
3.9	Proposed instructions for use as printed, or to be printed, on labels - always required	—		—	—
4.1.1	Description and specification of the packaging and materials used in packaging, size, capacity, size of openings, types of closure and seals - always required	—		—	—

Preparation: Active Substance(s): Applicant: Date:

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.1.2	Suitability of the packaging and closures				
	* Strength	—	—	—	—
	* Leakproofness	—	—	—	—
	* Resistance to normal transport and handling	—	—	—	—
	- always required				
4.1.3	Resistance of the packaging material to its contents - always required	—	—	—	—
4.2	Procedures for cleaning application equipment and protective clothing - always required	—		—	—
	Effectiveness of the cleaning procedures - always required	—	—	—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.3.1	Pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces				
	* Pre-harvest interval (in days) for each relevant crop	—		—	—
	* Re-entry period (in days) for livestock, to areas to be grazed	—		—	—
	* Re-entry period (in hours or days) for man to crops, buildings or spaces treated	—		—	—
	* Withholding period (in days) for animal feedingstuffs	—		—	—
	* Waiting period (in days) between application and handling treated products	—		—	—
	* Waiting period (in days) between last application and sowing or planting succeeding crops	—		—	—
	- required where risks to man or livestock may arise				
4.3.2	Information on any specific agricultural, plant health or environmental conditions under which the preparation may or may not be used - required where necessary in the light of test results	—		—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.4	Statement of the risks arising and the recommended methods, precautions and handling procedures to minimize those risks, relating to				
	* Warehouse storage	—		—	—
	* User level storage	—		—	—
	* Transport	—		—	—
	* Fire	—		—	—
	- always required				
	Protective clothing and equipment proposed				
	* Nature	—		—	—
	* Characteristics	—		—	—
	- always required				
	Sufficient data to evaluate the suitability and effectiveness of the protective clothing and equipment under realistic conditions of use - required where their use is proposed	—	—	—	—
	Procedures to minimize the generation of waste - always required	—		—	—
	Information on combustion products likely to be generated in the event of fire - required where the information is available	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.5	Detailed procedures for use in the event of an accident during transport, storage or use				
	* Containment of spillages	—		—	—
	* Decontamination of areas, vehicles and buildings	—		—	—
	* Disposal of damaged packaging, adsorbents and other materials	—		—	—
	* Protection of emergency workers and bystanders	—		—	—
	* First aid measures	—		—	—
	- always required				
4.6.1	Neutralization procedures (*e.g.* reaction with alkali to form less toxic compounds) for use in the event of accidental spillages				
	* Details of proposed procedures for small quantities	—		—	—
	* Evaluation of products of neutralization (small quantities)	—		—	—
	* Procedures for disposal of neutralized waste (small quantities)	—		—	—
	* Details of proposed procedures for large quantities	—		—	—
	* Evaluation of products of neutralization (large quantities)	—		—	—
	* Procedures for disposal of neutralized waste (large quantities)	—		—	—
	- required where such procedures are feasible				

Preparation: Active Substance(s): Applicant: Date:

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
4.6.2	Pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis - required for preparations with a halogen content greater than 60 %	—	—	—	—
	Detailed instructions for safe disposal of the plant protection product and its packaging - always required	—		—	—
4.6.3	Methods other than controlled incineration for disposal of the plant protection product, contaminated packaging and contaminated materials -				
	* Detailed description of such methods	—		—	—
	* Data to establish their effectiveness and safety	—		—	—
	- where available				

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 4** **Evaluation Form 4 Annex IIIA Test and Study Reports**

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5	* Samples of the preparation - required where requested	—		—	—
	* Analytical standards for pure active substance - required where requested	—		—	—
	* Samples of the active substance as manufactured - required where requested	—		—	—
	* Analytical standards for relevant metabolites and all other components included in the residue definition - required where requested	—	—	—	—
	* Samples of reference substances for relevant impurities - if available, required where requested	—	—	—	—
5.1.1	Description of analytical methods for the determination of the active substance in plant protection products - always required	—		—	—
	For preparations containing more than one active substance, a description of a method capable of determining each in the presence of the other	—		—	—
	- required where relevant - if a combined method is not submitted, the technical reasons for same must be stated				
	Applicability of existing CIPAC methods - always required	—	—	—	—
5.1.2	Description of analytical methods for the determination of impurities (non-active components arising from the manufacturing process or from degradation during storage) which are of toxicological, ecotoxicological or environmental concern, in the preparation - expert judgement required to determine if required	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Description of analytical methods for the determination of formulants or constituents of formulants in the plant protection product - always required where such compounds are of toxicological, ecotoxicological or environmental significance	—	—	—	—
5.1.3.1	For each method submitted -				
	* Specificity	—	—	—	—
	* Extent of interference by other substances present in the preparation	—	—	—	—
	* Explanation of interferences which contribute more than ± 3 % of the total quantity determined	—	—	—	—
	- always required				
5.1.3.2	For each method submitted, linearity over an appropriate range -				
	* Equation of the calibration line	—	—	—	—
	* Correlation co-efficient	—	—	—	—
	* Representative labelled documentation *e.g.* chromatograms	—	—	—	—
	- always required				
5.1.3.3	For each method submitted, accuracy -				
	* Pure active substance - always required	—	—	—	—
	* Impurities - required for toxicologically, ecotoxicologically or environmentally significant impurities in the preparation	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
5.1.3.4	For each method submitted, repeatability (at least 5 determinations) -				
	* % relative standard deviation (RSD) - always required	—	—	—	—
	* Indication as to whether outliers identified have been discarded - always required	—	—	—	—
	* reasons for the occurrence of outliers - must be attempted where outliers are discarded	—	—	—	—
5.2	Description of analytical methods for the determination of residues (all components included in the residue definition proposed (see point 8) to enable compliance with MRLs to be determined or to determine dislodgeable residues - always required	—	—	—	—
	For each method and representative matrix -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Validation - independent laboratory	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Description of methods for analysis of soil for parent compound and metabolites of toxicological, ecotoxicological or environmental concern - always required	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				
	Description of methods for analysis of water (drinking water, ground water and surface water) for parent compound and metabolites of toxicological, ecotoxicological or environmental concern - always required	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Description of methods for analysis of air for active substance and metabolites, formed during or shortly after application, of toxicological concern - required unless operator exposure, worker exposure or bystander exposure are unlikely to occur	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if appropriate)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				
	Analytical methods for parent compound and toxicologically, ecotoxicologically or environmentally significant metabolites in body fluids and tissues - required for active substances classified as *Toxic* or *Very Toxic*	—	—	—	—
	For each method -				
	* Specificity (using a confirmatory method, if necessary)	—	—	—	—
	* Repeatability	—	—	—	—
	* Limit of determination	—	—	—	—
	* Individual and mean recovery, overall standard deviation and relative standard deviation at each fortification level	—	—	—	—
	- required for each method reported				
6	Efficacy data - see subparagraph 3.1.2 (ii) and 3.2.2 (ii)				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.1.1	Acute oral toxicity - required unless for preparations containing a single active substance, it may be classified as being *Very Toxic, Toxic or Harmful,* in accordance with Article 3 (2) of Directive 78/631/EEC	—	—	—	—
7.1.2	Acute percutaneous toxicity - required unless for preparations containing a single active substance, it may be classified as being *Very Toxic, Toxic or Harmful,* in accordance with Article 3 (2) of Directive 78/631/EEC	—	—	—	—
7.1.3	Acute inhalation toxicity to rats - required where the preparation, or the smoke it generates, is . a gas or liquefied gas, . is a smoke generating formulation or fumigant, . is used with fogging equipment, . is a vapour releasing preparation, . is an aerosol, . is a powder containing a significant proportion of particles or diameter < 50 mm (> 1 % on a weight basis), . is to be applied from aircraft in cases where inhalation exposure is relevant, . contains an active substance with a vapour pressure > 1 x 10^{-2} Pa and is to be included in enclosed spaces such as warehouses or glasshouses, or . is to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 mm (> 1 % on a weight basis)	—	—	—	—
7.1.4	Skin irritation - required except where severe skin effects may be produced or effects can be excluded (see EEC Method B4)	—	—	—	—
7.1.5	Eye Irritation - required except where severe effects may be produced (see EEC Method B5)	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.1.6	Skin sensitization - required except where the active substance(s) or formulants are known to have sensitizing properties	—	—	—	—
7.1.7	Supplementary studies for combinations of plant protection products (tests as at points 7.1.1 to 7.1.6) - required in particular cases, where label recommendations require use with other plant protection products or adjuvants as a tank mix to achieve the desired effect, . depending on the results of the acute toxicity studies for the individual products, . the likelihood of exposure to the combination, and . available information or practical experience with the products concerned or similar products	—	—	—	—
7.2.1.1	Estimation of operator exposure assuming personal protective equipment is not used - always required	—		—	—
	Estimation of operator exposure assuming personal protective equipment is used - required where on the basis of the first estimate, it is clear that the AOEL or TLV may be exceeded	—		—	—
7.2.1.2	Measurement of operator exposure - required where on the basis of estimated exposure, either the AOEL or TLV may be exceeded, unless, where dermal exposure is the most important exposure route, a dermal absorption test (point 7.3) permits the estimate of operator exposure to be refined and when refined it is clear that the AOEL will not be exceeded	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.2.2	Estimation of bystander exposure assuming personal protective equipment is not used - always required	—	—	—	—
	Measurement of bystander exposure - required where on the basis of estimates, there is cause for concern	—	—	—	—
7.2.3.1	Estimation of worker exposure assuming personal protective equipment is not used - always required	—	—	—	—
	Estimation of worker exposure assuming personal protective equipment is used - required where on the basis of the first estimate, it is clear that the AOEL may be exceeded	—	—	—	—
	Estimation of worker exposure assuming personal protective equipment is used and using data generated on dislodgeable residues under the proposed conditions of use - required where on the basis of the second estimate, it is clear that the AOEL may be exceeded	—	—	—	—
7.2.3.2	Measurement of worker exposure - required where on the basis of estimated exposure, either the AOEL or TLV may be exceeded, unless, where dermal exposure is the most important exposure route, a dermal absorption test (point 7.3) permits the estimate of worker exposure to be refined and when refined it is clear that the AOEL will not be exceeded	—	—	—	—

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Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
7.3	Dermal absorption, *in vivo* in the rat - required where on the basis of estimated operator or worker exposure, it appears that either the AOEL or TLV may be exceeded	—	—	—	—
	Comparative dermal absorption, *in vitro* using rat and human skin - required where on the basis of estimated operator or worker exposure, refined with the benefit of data from the *in vivo* dermal absorption study, it appears that either the AOEL or TLV may be exceeded	—	—	—	—
7.4	Notification and safety data sheet submitted in the context of Directive 67/549/EEC and Commission Directive 91/155/EEC for each formulant - required where available	—	—	—	—
	Available toxicological data for each formulant - always required	—	—	—	—

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Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8	Stability of residues during storage of samples - required for . compounds known to be volatile or labile . samples not frozen within 24 hours of sampling or not analyzed within 30 days of sampling or in the case of radiolabelled material, not analyzed within 6 months of sampling	—	—	—	—
	Stability of residues in sample extracts - required where samples are not analyzed within 24 hours of extraction	—	—	—	—
8.1	Supplementary studies on metabolism, distribution and expression of residues in plants or livestock - required if it is not possible to extrapolate from the data provided in the context of points 6.1 and 6.2 of Annex IIA, *e.g.* for crops or for livestock for which data were not submitted for inclusion of the active substance in Annex I, or to amend the conditions of inclusion, or where it can be expected that a different metabolism will occur	—	—	—	—
8.2	Supplementary residue trials (supervised field trials) for crops or plant products used as food or feed on which use is proposed - if it is not possible to extrapolate from the data provided in the context of point 6.3 of Annex IIA, *e.g.* special formulations, different application methods, additional crops -				
	* Pre-harvest use on major crops - trials over two seasons are required; if use is proposed in both regions, at least 8 trials representative of the northern European region and a further 8 trials representative of the Mediterranean region, are required, unless it can be justified that there are no residues in the edible part of the plant, or unless extrapolation from adequate data on another crop is possible; the number of trials can be reduced where it can be justified that the residue levels in plants and plant products are lower than the LOQ; where a significant part of the consumable crop is present at time of application, residue disappearance curves for half of the trials are required	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Pre-harvest use on minor crops - trials over two seasons are required; if use is proposed in both regions, at least 4 trials representative of the northern European region and a further 4 trials representative of the Mediterranean region, are required, unless it can be justified that there are no residues in the edible part of the plant, or unless extrapolation from adequate data on another crop is possible; the number of trials can be reduced where it can be justified that the residue levels in plants and plant products are lower than the LOQ; where a significant part of the consumable crop is present at time of application, residue disappearance curves for half of the trials are required	—	—	—	—
	* Post-harvest uses - at least 4 trials carried out at different locations in one growing season and with different cultivars are required for each application method and store type, unless extrapolation from adequate data on another stored crop is possible	—	—	—	—
8.3	Supplementary livestock feeding studies - if it is not possible to extrapolate from the data provided in the context of point 6.4 of Annex IIA, *e.g.* use on additional fodder crops is to be authorized, leading to an increased intake of residues by livestock -				
	* Poultry and/or lactating ruminants (goat or cow) - required if . where significant residues occur in crops or part of the crop fed to animals (≥ 0.1 mg/kg of the total diet as received) except in special cases (*e.g.* accumulation of active substance), and . on the basis of the metabolism studies it is evident that significant residues (≥ 0.01 mg/kg or greater than the LOQ if that is > 0.01 mg/kg) occur in any edible animal tissue, taking into account the residue levels in potential feedingstuffs performed at the 1x dose rate	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Pigs - required where metabolic patterns in ruminants differ significantly from those in the rat, unless the expected intake by pigs is not significant	—	—	—	—
8.4	Supplementary studies on the effects of industrial processing and/or household preparation on residue levels - if it is not possible to extrapolate from the data provided in the context of point 6.5 of Annex IIA, *e.g.* crops for which data were not submitted for inclusion of the active substance in Annex I, or to amend the conditions of inclusion -				
	* Effects of industrial processing and/or household preparation (representative processing situations) on the nature of the residue - required unless . the plant or plant product is mostly eaten raw (except products with inedible portions such as citrus, banana or kiwi fruit), . the total TMDI is less than 10 % of the ADI, . no significant residues (> 0.1 mg/kg) occur in the plant or plant product to be processed, or . no analytically determinable residues occur in the plant or plant product processed - required for determinable residues below 0.1 mg/kg where the active substance has high acute toxicity or a low ADI	—	—	—	—
	* Distribution of the residue in peel/pulp - may be required for plant products with inedible portions such as citrus, banana or kiwi fruit	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	* Balance studies on a core set of representative processes - required unless . the plant or plant product is mostly eaten raw (except products with inedible portions such as citrus, banana or kiwi fruit), . the total TMDI is less than 10 % of the ADI, . no significant residues (> 0.1 mg/kg) occur in the plant or plant product to be processed, or . no analytically determinable residues occur in the plant or plant product processed				
	- required for determinable residues below 0.1 mg/kg where the active substance has high acute toxicity or a low ADI	—	—	—	—
	* Follow-up studies to determine concentration or dilution factors - required where the processed product is an important part of the diet and if a significant transfer of residue into the processed products could occur	—	—	—	—
8.5	Supplementary studies for residues in representative succeeding crops - required if it is not possible to extrapolate from the data provided in the context of point 6.6 of Annex IIA, *e.g.* special formulations, different application methods, additional crops	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.6	Proposed residue definition - always required	—	—	—	
	Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed, including details of statistical analyses used - always required	—	—	—	
8.7	Proposed pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces and a justification for each proposal				
	* Pre-harvest interval (in days) for each relevant crop	—	—	—	
	* Re-entry period (in days) for livestock, to areas to be grazed	—	—	—	
	* Re-entry period (in hours or days) for man to crops, buildings or spaces treated	—	—	—	
	* Withholding period (in days) for animal feedingstuffs	—	—	—	
	* Waiting period (in days) between last application and sowing or planting the crop to be protected	—	—	—	
	* Waiting period (in days) between application and handling treated products	—	—	—	
	* Waiting period (in days) between last application and sowing or planting succeeding crops	—	—	—	

- required where risks to man or livestock may arise

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Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
8.8	Estimation of the potential and actual exposure through diet and other means -				
	* TMDI calculations - always required	—	—	—	—
	* NEDI calculations - required unless the TMDI calculations demonstrate that the ADI will not be exceeded	—	—	—	—
8.9	Summary and evaluation of residue behaviour - always required	—		—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
9.1.1.1	Rate of degradation in soil - if it is not possible to extrapolate from the data provided for the active substance and relevant metabolites, degradation and reaction products in the context of point 7.1.1.2.1 of Annex IIA (*e.g.* slow release formulations) -				
	Aerobic degradation of the preparation in soil - required except where the manner of use of the preparation precludes soil contamination	—	—	—	—
	Anaerobic degradation of the preparation in soil - required if exposure to anaerobic conditions is likely following use of the preparation	—	—	—	—
9.1.1.2	Field studies -				
	Soil dissipation testing on a range of representative soils - normally 4 soils - required if it is not possible to extrapolate from the data provided in the context of point 7.1.1.2.2 of Annex IIA for the active substance and relevant metabolites, degradation and reaction products (*e.g.* slow release formulations), where DT_{50Lab} determined at 20 °C and a soil moisture content equivalent to a pF value of 2 - 2.5 > 60 days	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Soil residue testing - required if it is not possible to extrapolate from the data provided in the context of point 7.1.1.2.2 of Annex IIA for the active substance and relevant metabolites, degradation and reaction products (*e.g.* slow release formulations), where DT_{50Lab} is greater than ⅓ the period between application and harvest and where absorption by the succeeding crop is possible, unless - . soil residues at sowing or planting of a succeeding crop can be reliably estimated from the data on soil dissipation, or . it can be shown that the residues concerned will not be phytotoxic to or leave unacceptable residues in rotational crops	—	—	—	—
	Soil accumulation testing on 2 relevant soils - required if it is not possible to extrapolate from the data provided in the context of point 7.1.1.2.2 of Annex IIA for the active substance and relevant metabolites, degradation and reaction products (*e.g.* slow release formulations), where on the basis of soil dissipation studies $DT_{90f} > 1$ year and repeated application in the same or succeeding years is intended, unless reliable information can be provided using calculations (model) or another appropriate assessment	—	—	—	—
9.1.2.1	Mobility of the plant protection product in soil - Column leaching studies - required if it is not possible to extrapolate from the data provided in the context of point 7.1.2 and 7.1.3.1 of Annex IIA for the active substance and relevant metabolites, degradation and reaction products (*e.g.* slow release formulations)	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
9.1.2.2	Lysimeter studies - expert judgement required to decide whether lysimeter or field leaching studies are required	—	—	—	—
	Field leaching studies - expert judgement required to decide whether field leaching or lysimeter studies are required	—	—	—	—
	- a study is required where it is not possible to extrapolate from the data provided in the context of Annex IIA point 7.1.3 (*e.g.* slow release formulations)				
9.1.3	Predicted environmental concentrations in soil (PEC_s) for the active substance at the highest rate of application proposed and relating to the maximum number and highest rates of application proposed, for each relevant soil tested -				
	* Initial PEC_s value	—	—	—	—
	* Short-term PEC_s values - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Long-term PEC_s values - 7, 28, 50 and 100 days after last application	—	—	—	—
	- required where contamination of soil may occur				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Predicted environmental concentrations in soil (PEC_s) for relevant metabolites, degradation and reaction products, at the highest rate of application proposed and relating to the maximum number and highest rates of application proposed, for each relevant soil tested-				
	* Initial PEC_s value	—	—	—	—
	* Short-term PEC_s values - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Long-term PEC_s values - 7, 28, 50 and 100 days after last application	—	—	—	—
	- required where contamination of soil may occur				
9.2.1	Predicted environmental concentrations in ground water (PEC_{GW}) at the highest rate of application proposed and relating to the maximum number and highest rates of application proposed -				
	* Active substance	—	—	—	—
	* Relevant metabolites, degradation and reaction products	—	—	—	—
	- required where contamination of soil can occur				
	Additional field testing - expert judgement required to decide whether testing is required	—	—	—	—
9.2.2	Information on impact on water treatment procedures - required in the context of conditional authorizations to be granted in accordance with Annex VI, Part C, point 2.5.1.2 (b)	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
9.2.3	Predicted environmental concentrations in surface water (PEC_{sw}) for the active substance at the highest rate of application proposed and relating to the maximum number and highest rates of application proposed, relevant to lakes, ponds, rivers, canals, streams, irrigation/drainage canals and drains -				
	* Initial PEC_{sw} value for static water bodies	—	—	—	—
	* Initial PEC_{sw} value for slow moving water bodies	—	—	—	—
	* Short-term PEC_{sw} values for static water bodies - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Short-term PEC_{sw} values for slow moving water bodies - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Long-term PEC_{sw} values for static water bodies - 7, 14, 21, 28, 42 days after last application	—	—	—	—
	* Long-term PEC_{sw} values for slow moving water bodies - 7, 14, 21, 28, 42 days after last application	—	—	—	—
	- required where contamination of surface water may occur				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Predicted environmental concentrations in surface water (PEC_{sw}) for relevant metabolites, degradation and reaction products at the highest rate of application proposed and relating to the maximum number and highest rates of application proposed, relevant to lakes, ponds, rivers, canals, streams, irrigation/drainage canals and drains -				
	* Initial PEC_{sw} value for static water bodies	—	—	—	—
	* Initial PEC_{sw} value for slow moving water bodies	—	—	—	—
	* Short-term PEC_{sw} values for static water bodies - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Short-term PEC_{sw} values for slow moving water bodies - 24 hours, 2 days and 4 days after last application	—	—	—	—
	* Long-term PEC_{sw} values for static water bodies - 7, 14, 21, 28, 42 days after last application	—	—	—	—
	* Long-term PEC_{sw} values for slow moving water bodies - 7, 14, 21, 28, 42 days after last application	—	—	—	—
	- required where contamination of surface water can occur				
	Additional field testing - expert judgement required to decide whether testing is required	—	—	—	—
9.3	Fate and behaviour in air - requirements being developed				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.1	Acute toxicity exposure ratio (TER_A) for birds - required unless exposure of birds can be precluded (*e.g.* use in enclosed spaces, wound healing treatments)	—	—	—	—
	Short-term toxicity exposure ratio (TER_{ST}) for birds - required unless exposure of birds can be precluded (*e.g.* use in enclosed spaces, wound healing treatments)	—	—	—	—
	In the case of baits, the concentration of active substance in the bait in mg/kg - always required	—	—	—	—
	In the case of pellets, granules, prills or treated seed -				
	* Amount of the active substance in or on each pellet, granule, prill or treated seed	—	—	—	—
	* Proportion of the LD_{50} for the active substance in 100 particles and per gram of particles	—	—	—	—
	- always required				
	In the case of pellets, granules, and prills, their size and shape - always required	—	—	—	—
10.1.1	Acute oral toxicity of the preparation to the more sensitive of the species identified in tests with the active substance (Annex IIA points 8.1.1 and 8.1.2) - required where TER_A or TER_{ST} for the active substance are between 10 and 100 or where results from testing in mammals provided evidence of significantly greater toxicity of the preparation compared to the active substance, unless it is justified that birds are unlikely to be exposed to the plant protection product	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.1.2	Supervised cage or field trials - required where the TER_A or $TER_{ST} \leq 10$ or the $TER_{LT} \leq 5$ for the active substance - expert judgement required where TER_A or TER_{ST} for the active substance is between 10 and 100 - not required where TER_A or TER_{ST} for the active substance is > 100 and there is no evidence of risk from any further study on the active substance (*e.g.* reproduction study - Annex IIA point 8.1.3)	—	—	—	—
10.1.3	Acceptance of bait, granules or treated seeds by birds (palatability test) - required for seed dressings, baits and granules, where the TER_A for the active substance ≤ 10	—	—	—	—
10.1.4	Effects of secondary poisoning - expert judgement required to decide when required	—	—	—	—

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Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.2	Toxicity exposure ratios for aquatic species				
	* TER_A for fish	—	—	—	—
	* TER_{LT} for fish	—	—	—	—
	* TER_A for Daphnia	—	—	—	—
	* TER_{LT} for Daphnia	—	—	—	—
	* TER_A for an aquatic insect species	—	—	—	—
	* TER_{LT} for an aquatic insect species	—	—	—	—
	* TER_A for an aquatic crustacean species	—	—	—	—
	* TER_{LT} for an aquatic crustacean species	—	—	—	—
	* TER_A for an aquatic gastropod mollusc species	—	—	—	—
	* TER_{LT} for an aquatic gastropod mollusc species	—	—	—	—
	* TER_{LT} for algae	—	—	—	—
	- required where contamination of water can occur, for both static and slow moving water bodies				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.2.1	Acute toxicity (aquatic) of the preparation - unless testing in accordance with point 10.2.4 is reported, required for one species from each group (fish, aquatic invertebrate and algae), if the plant protection product itself can contaminate water, where - . the acute toxicity of the preparation cannot be predicted on the basis of data on the active substance - especially the case if the formulation contains more than one active substance, or formulants such as solvents, emulgators, surfactants dispersants or fertilizers which may enhance toxicity, or . the intended use includes direct application to water - except where information found during testing with the active substance (Annex IIA point 8.2.1, 8.2.4, 8.2.6) is indicative of one group being significantly more sensitive, when testing on a species from that group suffices	—	—	—	—
10.2.2	Microcosm or mesocosm study - required where $TER_A \leq 100$ or where $TER_{LT} \leq 10$. Expert judgement is required to decide whether a microcosm or mesocosm study is appropriate	—	—	—	—
10.2.3	Residue data in fish (long term microcosm or mesocosm study) - expert judgement is necessary to decide when required	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.2.4	Chronic toxicity (28 day exposure) to juvenile fish - expert judgement necessary to determine if required in circumstances where testing with the active substance was required and if it is not possible to extrapolate from data relevant to the active substance (Annex IIA point 8.2.2.1)	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
	Fish early life stage toxicity test - expert judgement necessary to determine if required in circumstances where testing with the active substance was required and if it is not possible to extrapolate from data relevant to the active substance (Annex IIA point 8.2.2.2)	—	—	—	—
	Analytical data on concentrations in the test media - required for all tests reported	—	—	—	—
	Fish life cycle test - expert judgement necessary to determine if required in circumstances where testing with the active substance was required and if it is not possible to extrapolate from data relevant to the active substance (Annex IIA point 8.2.2.3)	—	—	—	—
	Chronic toxicity to aquatic invertebrates -				
	* Chronic toxicity in *Daphnia magna* (21-day)	—	—	—	—
	* Chronic toxicity for a representative species of aquatic insects	—	—	—	—
	* Chronic toxicity for a representative species of aquatic gastropod molluscs	—	—	—	—
	- expert judgement necessary to determine if required in circumstances where testing with the active substance was required and if it is not possible to extrapolate from data relevant to the active substance (Annex IIA point 8.2.5)				

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.3	Effects on terrestrial vertebrates other than birds				
	* Acute toxicity exposure ratio (TER_A) - required unless it is justified that direct or indirect exposure is unlikely (*e.g.* use in enclosed spaces)	—	—	—	—
	* Short-term toxicity exposure ratio (TER_{ST}) - required unless it is justified that direct or indirect exposure is unlikely (*e.g.* use in enclosed spaces)	—	—	—	—
	* Long-term toxicity exposure ratio (TER_{LT}) - required unless it is justified that direct or indirect exposure is unlikely (*e.g.* use in enclosed spaces)	—	—	—	—
	Toxicity to terrestrial vertebrates other than birds, where the required information is not provided by testing in accordance with Annex II, section 5, and Annex III, section 7 and where exposure is likely -				
	* Acute oral toxicity of the preparation	—	—	—	—
	* Acceptance of bait, granules or treated seeds by terrestrial vertebrates (palatability test)	—	—	—	—
	* Effects of secondary poisoning	—	—	—	—
	- not required where TER_A or TER_{ST} > 100 for the active substance and there is no evidence of risk from any other study - expert judgement required in other cases				
	* Supervised cage or field trials or other appropriate studies - required where the TER_A or $TER_{ST} \leq 10$ or $TER_{LT} \leq 5$ for the active substance	—	—	—	—

Preparation: Active Substance(s): Applicant: Date:

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.4	Hazard Quotients for bees				
	* Oral exposure Q_{HO}	—	—	—	—
	* Contact exposure Q_{HC}	—	—	—	—
	- required unless the preparation is for exclusive use in situations where bees are unlikely to be exposed . food storage in enclosed spaces . non-systemic seed dressings . non-systemic preparations for application to soil . non-systemic dipping treatments for transplanted crops and bulbs . wound sealing and healing treatments . rodenticidal baits . use in glasshouses without pollinators				
10.4.1	Acute toxicity of the preparation to bees -				
	* Acute oral toxicity	—	—	—	—
	* Acute contact toxicity	—	—	—	—
	- required the preparation contains more than 1 active substance, or - required if the toxicity of the preparation cannot be reliably predicted to be the same or lower than a preparation tested in accordance with Annex IIA point 8.3.1.1 or this point				
10.4.2	Effects on bees of residues on crops - where $Q_{HC} \geq 50$, expert judgement required to determine if testing is required, unless there are no significant residues on crops which could effect foraging bees or sufficient information is available from testing in accordance with points 10.4.3, 10.4.4 and 10.4.5	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.4.3	Cage tests - where conducted they must be reported - required where the Q_{HO} and Q_{HC} are > 50 - not required where field tests are conducted (point 10.4.4) - not required where the Q_{HO} and Q_{HC} are < 50, unless significant effects are observed in the bee brood feeding test (Annex IIA point 8.3.1.2), or if there are indications of indirect effects such as intoxication through nectar, pollen or other residues, delayed action or modification of bee behaviour	—	—	—	—
10.4.4	Field tests - taking account of the proposed manner of use and fate and behaviour of the active substance, required where on the basis of expert judgement, significant effects are seen in cage testing	—	—	—	—
	Investigation of special effects -				
	* Larval toxicity	—	—	—	—
	* Long residual effects	—	—	—	—
	* Disorienting effects on bees	—	—	—	—
	- required where on the basis of expert judgement, effects identified in field testing require further investigation				
10.4.5	Tunnel testing to investigate effects of feeding on contaminated honey dew or flowers - required where it is not possible to investigate certain effects in cage or field trials *e.g.* preparations for control of aphids and other sucking insects	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.5.1	**Effects on arthropods other than bees** - not required where > 99 % effect can be predicted from relevant available data - not required where preparations containing the active substance are for exclusive use in situations where exposure does not occur . food storage in enclosed spaces . wound sealing and healing treatments . rodenticidal baits - required when significant effects were observed (≥ 30 %) in the Annex IIA point 8.3.2 tests - required if . the preparation contains more than 1 active substance . the toxicity of a new preparation cannot be reliably predicted to be the same or lower than the formulation tested in accordance with Annex IIA point 8.3.2 or this point . continued or repeated exposure can be anticipated . there is a significant change in the proposed use (*e.g.* from arable crops to orchards) and species relevant to the new use have not been tested . an increase in the recommended application rate, compared to that tested under Annex IIA point 8.3.2, is proposed **Effects on the 2 most sensitive species already tested, using artificial substrates** - required for new mixtures or formulations, where effects seen in testing in accordance with Annex IIA point 8.3.2 were > 30 % but < 99 %	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
	Effects on the 2 additional species relevant to the proposed uses of the preparation, using artificial substrates - required where effects seen in testing in accordance with Annex IIA point 8.3.2 were > 30 % but < 99 %, or - required in the case of a change of use (*e.g.* from arable crops to orchards) - also required for new mixtures or formulations, where the new mixture or formulation is significantly more toxic than that tested in accordance with Annex IIA point 8.3.2	—	—	—	—
	Effects on non-target terrestrial arthropods in extended laboratory tests - expert judgement required to determine when required	—	—	—	—
	Effects on non-target terrestrial arthropods in semi-field tests - expert judgement required to determine when required	—	—	—	—
10.5.2	Field tests on arthropod species - expert judgement required to determine if testing is necessary	—	—	—	—
10.6.1	Toxicity exposure ratios for earthworms, TER_A and TER_{LT} - required, unless it is justified that direct or indirect exposure is unlikely	—	—	—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.6.1.1	**Acute toxicity to earthworms** - required, unless it is justified that direct or indirect exposure is unlikely, where . the preparation contains more than 1 active substance . the toxicity of a new preparation cannot be reliably predicted from the formulation tested in accordance with Annex IIA point 8.4 or this point	—	—	—	—
10.6.1.2	**Sublethal effects on earthworms** - required, unless it is justified that direct or indirect exposure is unlikely, where . the preparation contains more than one active substance . the toxicity of a new formulation cannot be reliably predicted form tests carried out in accordance with Annex IIA point 8.4 or this point . the application rate is to be increased relevant to that previously tested	—	—	—	—
10.6.1.3	**Field tests (effects on earthworms)** - required, unless it is justified that direct or indirect exposure is unlikely, where the long-term toxicity/exposure ratio for the active substance (TER_{LT}) < 5	—	—	—	—
	Residue content of earthworms - expert judgement necessary to determine if required	—	—	—	—

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.6.2	Effects on other soil non-target macro-organisms - required unless . DT_{90} values determined in accordance with point Annex IIIA, point 9.1 are less than 100 days, . the nature of the preparation or its manner of use are such that exposure does not occur, or . relevant Annex IIA data (points 8.3.2, 8.4 and 8.5) indicates that a risk does not arise for earthworms, soil macroflora or soil microflora	—	—	—	—
	Effect on organic matter breakdown - required where DT_{90f} values determined in accordance with Annex IIIA point 9.1 are > 365 days	—	—	—	—
10.7.1	Laboratory test to investigate impact on soil microbial activity - required where DT_{90f} values determined in accordance with Annex IIIA point 9.1 > 100 days, unless deviations from the control values in testing in accordance with Annex IIA point 8.5 after 100 days < 25 % and the data generated is relevant to the preparation, its uses and manner of use	—	—	—	—
10.7.2	Further laboratory, glasshouse of field testing to investigate impact on soil microbial activity - may be required where at the end of 100 days, measured activity deviates by more than 25 % in laboratory testing	—	—	—	—

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
10.8	Summary of available data from preliminary tests used to assess biological activity and dose range finding, which may provide information on other non-target species (flora and fauna) - required where available	—	—	—	—
	A critical assessment as to the relevance of the preliminary test data to potential impact on non-target species - required where preliminary test data is available	—	—	—	—

Appendix 11 **Forms for use in checking dossiers for completeness** **Part 4** **Evaluation Form 4 Annex IIIA Test and Study Reports**

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
11	Summary and evaluation of points 9 and 10, together with a detailed and critical assessment of the data to include -				
	* Predicted distribution and fate in the environment and the time courses involved	—		—	—
	* Non-target species at risk and extent of potential exposure	—		—	—
	* Short and long term risks for non-target species, populations, communities and processes	—		—	—
	* Risk of fish kills and fatalities in large vertebrates or terrestrial predators	—		—	—
	* Precautions necessary to avoid or minimize contamination of the environment and for the protection of non-target species	—		—	—
	- always required				

Preparation: **Active Substance(s):** **Applicant:** **Date:**

Annex IIIA point	Information, test or study - circumstances in which required	Information, test or study provided Y/P/N	Justification provided L/N	Undertaking provided Date/N	Official use only Data Gap Y/N
12.1	Information on authorizations in other countries (see Initial Evaluation Form 1 - document D-2) - always required	—		—	—
12.2	Information on established MRLs in other countries (see Initial Evaluation Form 1 - documents E-1 and E-2) - always required	—		—	—
12.3	Justified proposals for the classification and labelling of the preparation according to Directive 67/548/EEC and Directive 78/631/EEC				
	* Hazard symbol(s)	—		—	—
	* Indications of danger	—		—	—
	* Risk phrases	—		—	—
	* Safety phrases	—		—	—
	- always required				
12.4	Proposals for risk and safety phrases in accordance with Article 15 (1), (g) and (h) - always required	—		—	—
	Proposed label (see Initial Evaluation Form 1 - document C) - always required	—		—	—
12.5	Specimens of proposed packaging - required where application is being made for the auhorization of plant protection product	—		—	—

Part 5 **Evaluation Form 5 -**

for use in checking that the *Tier 1* quality checks for individual tests and studies are of acceptable quality [18]

Active Substance
Applicant:
Date:

Test or Study Point	Description of the requirement	Provided Y/N[#]
1.1	The Annex II or Annex III point addressed	
1.2	A descriptive title of the type of test or study	
2	Reference point (location) of the report in the dossier (*e.g.* volume, section and Annex point)	
3.1	The names of the authors	
3.2	The title of the report	
3.3	The owner of the test or study report	
3.4	An indication as to whether it is a published or unpublished report	
3.5	The report number	
3.6	The date of the report	
4.1	The name and address of the testing facility	
4.2	The laboratory report/project number	
5.1	The dates of commencement and completion of experimental work	
5.2	A statement of the objectives of the test or study	
6.1	The identity of the test substance or material (ISO common name, batch number and degree of purity)	
6.2	An explicit reference to the relevant specification of composition of the test substance or material	
6.3	Where available, data relevant to the storage stability of the test substance or material	

[#] Y = yes; N = no

[18] Relevant for tests and studies for which the test methods used were not those currently specified (*e.g.* certain older studies)

Active Substance: **Applicant:** **Date:**

Test or Study Title: **Annex Point:**

Test or Study Point	Description of the requirement	Provided Y/N
6.4	Where relevant and available, data as to the stability of the test substance or material in the dosing vehicle	
6.5	Where relevant and available, data as to the homogeneity of the test substance or material in the dosing or testing vehicle	
6.6	Where data relating to the stability or homogeneity of the test substance is not available (*e.g.* certain older studies), a justification of the scientific validity of the study	
6.7	Where relevant, information as to the physical form of the test substance or material	
6.8	Full details of the composition of any dosing vehicles or solvents used	
7.1	The identity of the test method used	
7.2	Where not a method specified in Annex II, or Annex III, a reasoned justification for the choice of method used in terms of its scientific validity and comparability with the method specified in Annex II or Annex III	
7.3	On request, a copy of the method - full details of methods used which are unlikely to be accessible to competent authority of the Member State to which the dossier is submitted, should be attached to the study or test report	
7.4	Where test guidelines provide choice as to the method to be used, a reasoned justification for the choice made	
7.5	Where deviations from the test guidelines specified, or from other methods used, are employed, a description of and reasoned justification for the deviations	
8.1	Where relevant, an indication as to whether, or not, the test or study has been conducted by a laboratory certified as to its competence to conduct the test or study in compliance with the principles of GLP	
8.2	Where relevant, the certifying authority	
8.3	Where applicable, an indication as to whether, or not, the principles of GLP have been complied with	
8.4	Where relevant, a justification for non compliance with the principles of GLP	

Active Substance: **Applicant:** **Date:**

Test or Study Title: **Annex Point:**

Test or Study Point	Description of the requirement	Provided Y/N
9.1	Where relevant, a clear statement that the requirements of points 2.2 and 2.3 of the introduction to Annex III have been complied with - Good Experimental Practice (GEP)	
9.2	Where the requirements of points 2.2 and 2.3 of the introduction to Annex III apply, whether conducted by an official or an officially recognized testing facility or organization	
9.3	Where relevant, a justification for non compliance with the requirements of points 2.2 and 2.3 of the introduction to Annex III	
10	A description of the test system	
11	The identity of any statistical and other techniques applied to the data to aid interpretation, together with adequate documentation thereof and a justification for the use of the technique selected where non standard techniques are used	
12.1	Where reference to published papers is made in *Tier I* checks as to the quality of individual test and study reports, the bibliographic references concerned	
12.2	On request, copies of the papers concerned	
13	Where reference to unpublished data is made in *Tier I* checks as to the quality of individual test and study reports (*e.g.* historical control data on strains of test animals) a summary of such data	

Assessment of the Acceptability of the Quality of the Report

Report of acceptable quality ☐ Yes ☐ No

Comments:

Signature:

Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies [19]

Annex IIA point	Description of the test or study	Guideline specified [20]	Choice of method provided by guideline	GLP or GEP applicable
1.11	Analytical profile of batches			GLP
2.1.1	Melting/Freezing temperature	EEC A.1	Yes	GLP
2.1.2	Boiling temperature	EEC A.2	Yes	GLP
2.1.3	Decomposition of sublimation temperature	EEC A.2	Yes	GLP
2.2	Relative density	EEC A.3	Yes	GLP
2.3.1	Vapour Pressure	EEC A.4	Yes	GLP
2.3.2	Volatility (Henry's law constant)			GLP
2.5	Spectra (UV/VIS, IR, NMR, MS), molecular extinction at relevant wavelengths			GLP
2.6	Water solubility	EEC A.6	Yes	GLP
2.7	Solubility in organic solvents			
2.8	Partition coefficient	EEC A.8	Yes	GLP
2.9.1	Abiotic degradation hydrolysis as a function of pH	EEC C.7	No	GLP

[19] For reference purposes in completing Evaluation Form 5

[20] OJ L 133, means Commission Directive 88/302/EEC, OJ No L 133 of 30 May 1988

Appendix 11 Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
2.9.2	Direct phototransformation in water	SETAC [21]	N0	GLP
2.9.3	Quantum yield of direct phototransformation in water	SETAC [21]	N0	GLP
2.9.4	Dissociation constants in water	OECD 112	Yes	GLP
2.10	Photochemical oxidative degradation			GLP
2.11.1	Flammability (solids)	EEC A.10	No	GLP
	Flammability (gases)	EEC A.11	No	GLP
	Flammability (contact with water)	EEC A.12	No	GLP
2.11.2	Auto-ignition temperature (liquids and gases)	EEC A.15	No	GLP
	Relative self-ignition temperature for solids	EEC A.16	No	GLP
	UN-Bowes-Cameron-Cage-Test (UN-Recommendations on the Transport of Dangerous Goods, Chapter 14)	No 14.3.4	No	GLP
2.12	Flash point - closed cup methods only	EEC A.9	Yes	GLP
2.13	Explosive properties	EEC A.14	No	GLP
2.14	Surface tension	EEC A.5	Yes	GLP
2.15	Oxidizing properties (solids)	EEC A.17	No	GLP
3.8.1	Pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis			GLP

[21] Procedures for assessing the environmental fate and ecotoxicity of pesticides. SETAC-Europe, 1995. ISBN number 90-5607-002-9

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
3.8.2	Effectiveness of methods other than controlled incineration for disposal of the active substance, contaminated packaging and contaminated materials			
5.1	Toxicokinetic studies -			
	* Single dose, oral route, in rats	OJ L 133 (p 51)	No	GLP
	* Second single dose, oral route, in rats	OJ L 133 (p 51)	No	GLP
	* Repeated dose, oral route, in rats	OJ L 133 (p 51)	No	GLP
5.2.1	Acute toxicity (oral)	EEC B.1 or B.1 bis	Yes	GLP
5.2.2	Acute toxicity (dermal)	EEC B.3	No	GLP
5.2.3	Acute toxicity (inhalation)	EEC B.2	No	GLP
5.2.4	Acute toxicity (skin irritation)	EEC B.4	No	GLP
5.2.5	Acute toxicity (eye irritation)	EEC B.5	No	GLP
5.2.6	Skin sensitization	EEC B.6	Yes	GLP
5.3.1	Repeated dose (28 days) toxicity (oral)	EEC B.7	No	GLP
5.3.2	Sub-chronic oral toxicity test: 90-day repeated oral dose using rodent species	OJ L 133 (p 8)	No	GLP
	Sub-chronic oral toxicity test: 90-day repeated oral dose using non-rodent species	OJ L 133 (p 12)	No	GLP
	Sub-chronic oral toxicity test: 12 month repeated oral dose using non-rodent species			GLP

Appendix 11 Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
5.3.3	Repeated dose (28-days) toxicity (inhalation)	EEC B.8	No	GLP
	Sub-chronic inhalation toxicity test: 90-day repeated inhalation dose study using rodent species	OJ L 133 (p 20)	No	GLP
	Repeated dose (28-days) toxicity (dermal)	EEC B.9	No	GLP
	Sub-chronic dermal toxicity test: 90-day repeated dermal dose study using rodent species	OJ L 133 (p 16)	No	GLP
5.4.1	Mutagenicity (*Salmonella Typhimurium* - reverse mutation assay)	EEC B.14	No	GLP
	Mutagenicity (*in vitro* - mammalian cytogenetic test)	EEC B.10	No	GLP
	In vitro mammalian cell gene mutation test	OJ L 133 (p 61)	No	GLP
5.4.2	Mutagenicity (micronucleus test)	EEC B.12	No	GLP
	Mouse spot test	OJ L 133 (p 82)	No	GLP
	Mutagenicity (*in vivo* mammalian bone-marrow cytogenetic test, chromosomal analysis)	EEC B.11	No	GLP
5.4.3	Rodent dominant lethal test	OJ L 133 (p 76)	No	GLP
	In vivo mammalian germ cell cytogenetics	OJ L 133 (p 79)	No	GLP
	Mouse heritable translocation	OJ L 133 (p 85)	No	GLP
5.5	Chronic toxicity test	OJ L 133 (p 27)	No	GLP
	Carcinogenicity test	OJ L 133 (p 32)	No	GLP
	Combined chronic toxicity/carcinogenicity test	OJ L 133 (p 37)	No	GLP
	Mechanistic studies			GLP

Appendix 11 **Part 6** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies**

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
5.6.1	Two-generation reproductive toxicity test	OJ L 133 (p 47)	No	GLP
	Separate male and female reproductive toxicity tests			GLP
	Three segment design studies			GLP
	Dominant lethal assay for male fertility			GLP
	Cross-matings of treated males with untreated females and *vice versa*			GLP
	Effect on spermatogenesis			GLP
	Effects on oogenesis			GLP
	Sperm motility, mobility and morphology			GLP
	Investigation of hormonal activity			GLP
5.6.2	Teratogenicity test - rodent and non-rodent	OJ L 133 (p 24)	No	GLP
5.7	Acute delayed neurotoxicity of organophosphorous substances	OECD 418	No	GLP
5.8.1	Toxicity studies on metabolites			GLP
5.8.2	Supplementary studies on the active substance			GLP
6.1	Metabolism, distribution and expression of residues in plants	Commission Guidelines [22]		GLP
6.2	Metabolism, distribution and expression of residues in livestock	Commission Guidelines [22]		GLP

[22] Commission document 1607/VI/97 - rev 1 of 22 July 1997, Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market

Appendix 11 Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
6.3	Residue trials (supervised field trials)	Commission Guidelines [22]		GLP
6.4	Livestock feeding studies	Commission Guidelines [22]		GLP
6.5.1	Effects of industrial processing and/or household preparation (representative processing situations) on the nature of the residue	Commission Guidelines [22]		GLP
6.5.2	Effects of industrial processing and/or household preparation on residue levels	Commission Guidelines [22]		GLP
6.6	Estimates of residues in succeeding crops	Commission Guidelines [22]		
	Residue trials in succeeding crops	Commission Guidelines [22]		GLP
6.9	Estimation of potential and actual exposure through the diet and other means	WHO Guidelines [23]		
7.1.1.1.1	Aerobic degradation (route) in soil	SETAC [21]	No	GLP
7.1.1.1.2	Anaerobic degradation (route) in soil	SETAC [21]	No	GLP
	Soil photolysis	SETAC [21]		
7.1.1.2.1	Aerobic degradation (rate) in soil	SETAC [21]	No	GLP
	Anaerobic degradation (rate) in soil	SETAC [21]		GLP
7.1.1.2.2	Soil (field) dissipation studies	SETAC [21]	No	GLP
	Soil (field) residue studies	SETAC [21]	No	GLP
	Soil (field) accumulation studies		No	GLP

[23] Guidelines for predicting dietary intake of pesticide residues, WHO, 1989;

Application of risk analysis to food standards issues, Report of the Joint FAO/WHO Expert Consultation, Geneva, Switzerland, 13-17 March 1995 (WHO/FNU/FOS/95.3);

Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues, Report of a FAO/WHO Consultation, 1995 (WHO/FNU/FOS/95.11)

Appendix 11 **Part 6** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies**

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
7.1.2	Adsorption/desorption	OECD 106	No	GLP
7.1.3.1	Column leaching studies	SETAC [21]	Yes	GLP
7.1.3.2	Aged residue column leaching studies	SETAC [21]	No	GLP
7.1.3.3	Lysimeter studies	SETAC [21]	Yes	GLP
	Field leaching studies	SETAC [21]	Yes	GLP
7.2.1.1	Abiotic degradation hydrolysis as a function of pH	EEC C.7	No	GLP
7.2.1.2	Direct phototransformation in water	SETAC [21]	No	GLP
	Quantum yield of direct phototransformation in water	SETAC [21]	No	GLP
7.2.1.3.1	Biodegradation: determination of "ready" biodegradability	EEC C.4	Yes	GLP
7.2.1.3.2	Water/sediment study	SETAC [21]	No	GLP
7.2.1.4	Degradation in the saturated zone			GLP
8.1.1	Avian acute oral toxicity test	SETAC [21]	No	GLP
8.1.2	Avian dietary toxicity (5-day) test	OECD 205	No	GLP
8.1.3	Avian subchronic and reproductive toxicity test	OECD 206	No	GLP
8.2.1	Acute toxicity for fish	EEC C.1	No	GLP
8.2.2.1	Chronic (28-day) toxicity to juvenile fish			GLP
8.2.2.2	Fish early life stage toxicity test	OECD 210	No	GLP
8.2.2.3	Fish life cycle test			GLP
8.2.3	Bioaccumulation: flow through fish test	OECD 305E	No	GLP

Appendix 11 Part 6 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
8.2.4	Acute toxicity for *Daphnia*	EEC C.2	No	GLP
	Acute toxicity for aquatic insects			GLP
	Acute toxicity for aquatic crustaceans			GLP
	Acute toxicity for aquatic gastropod molluscs			GLP
8.2.5	*Daphnia* sp. reproduction test - 21 day	OECD 202 Part II	No	GLP
	Aquatic insect chronic toxicity/reproduction test			GLP
	Aquatic gastropod mollusc chronic toxicity/ reproduction test			GLP
8.2.6	Algal inhibition test	EEC C.3	No	GLP
8.2.7	Acute toxicity to sediment dwelling organisms			GLP
	Chronic toxicity to sediment dwelling organisms			GLP
8.2.8	Effects on aquatic plants			GLP
8.3.1.1	Honeybee acute oral toxicity test	EPPO 170	No	GEP-GLP [24]
	Honeybee acute contact toxicity test	EPPO 170	No	GEP-GLP [24]
8.3.1.2	Honeybee brood feeding test	ICPBR	No	GEP-GLP [24]
8.3.2	Effects on non-target terrestrial arthropods using artificial substrates	SETAC-ESCORT		GEP-GLP [24]
	Effects on non-target terrestrial arthropods in extended laboratory tests	SETAC-ESCORT		GEP-GLP [24]
	Effects on non-target terrestrial arthropods in semi field tests	SETAC-ESCORT		GEP-GLP [24]

[24] At the discretion of the Member State in which they are conducted, tests started on or before 31 December 1999, to be conducted in accordance with the principles of GEP, thereafter to be conducted in accordance with the principles of GLP

Appendix 11 **Part 6** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIA tests and studies**

Annex IIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
8.4.1	Earthworm, acute toxicity test	OJ L 133 (p 95)	No	GLP
8.4.2	Sublethal effects on earthworms			GLP
8.5	Impact on soil microbial activity	SETAC [21]		GLP
	Rates of recovery following treatment	SETAC [21]		GLP
8.6	Effects on other non-target organisms believed to be at risk			
8.7	Effects on biological methods for sewage treatment			GLP

Part 7 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies [25]

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
2.2.1	Explosive properties	EEC A.14	No	GLP
2.2.2	Oxidizing properties (solids)	EEC A.17	No	GLP
2.3	Flash point - closed cup methods only	EEC A.9	Yes	GLP
	Flammability (solids)	EEC A.10	No	GLP
	Flammability (gases)	EEC A.11	No	GLP
	Flammability (contact with water)	EEC A.12	No	GLP
	Auto-ignition temperature (liquids and gases)	EEC A.15	No	GLP
	Relative self-ignition temperature for solids	EEC A.16	No	GLP
	UN-Bowes-Cameron-Cage-Test (UN-Recommendations on the Transport of Dangerous Goods, Chapter 14)	No 14.3.4	No	GLP
2.4.1	Free acidity or alkalinity	CIPAC MT 31	Yes	GLP
	Determination of pH values	CIPAC MT 75	Yes	GLP
2.4.2	Determination of pH values	CIPAC MT 75	Yes	GLP
2.5.1	Viscosity of liquids	OECD 114	Yes	GLP
2.5.2	Viscosity of non newtonian liquids			GLP
2.5.3	Surface tension	EEC A.5	Yes	GLP
2.6.1	Relative density	EEC A.3	Yes	GLP

[25] For reference purposes in completing Evaluation Form 5

Appendix 11 **Part 7** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies**

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
2.6.2	Bulk (tap) density	CIPAC MT 33, 159 or 169	Yes	
2.7.1	Accelerated storage tests by heating	CIPAC MT 46	Yes	GLP [26]
	Minimum content after heat stability testing			GLP [26]
2.7.2	Low temperature stability	CIPAC MT 39, 48, 51 or 54	Yes	
2.7.3	Shelf life following storage at ambient temperature	GIFAP Method [27]		
2.8.1	Wettability of dispersible powders	CIPAC MT 53.3	Yes	
2.8.2	Persistent foaming	CIPAC MT 47	Yes	
2.8.3	Suspensibility	CIPAC MT 15, 161 or 168	Yes	
	Spontaneity of dispersion	CIPAC MT 160 or 174	Yes	
2.8.4	Dilution stability	CIPAC MT 41	No	
2.8.5	Dry sieve test	CIPAC MT 59.1	No	
	Wet sieve test	CIPAC MT 59.3 or 167	Yes	
2.8.6.1	Particle size distribution	OECD 110	Yes	GLP
	Nominal size range of granules	CIPAC MT 58.3 or 170	Yes	GLP

[26] GLP required only if on the basis of theoretical considerations, hazardous compounds may be formed during storage

[27] GIFAP Monograph No. 17

Appendix 11 **Part 7** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies**

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
2.8.6.2	Dust content	CIPAC MT 171	Yes	GLP
	Particle size distribution	OECD 110	Yes	GLP
2.8.6.3	Friability and attrition characteristics of granules			
2.8.7.1	Emulsion characteristics of emulsifiable concentrates	CIPAC MT 36	Yes	
	Stability of diluted emulsions	CIPAC MT 173	No	
2.8.7.2	Stability of dilute emulsions	CIPAC MT 20 or 173	Yes	
2.8.8.1	Flowability of granules	CIPAC MT 172	No	
2.8.8.2	Pourability (including rinsed residue) of suspensions	CIPAC MT 148	No	
2.8.8.3	Dustability after accelerated storage	CIPAC MT 34	No	
2.9.1	Physical compatibility of tank mixes			
2.9.2	Chemical compatibility of tank mixes			
2.10	Distribution on seeds	CIPAC MT 175		
	Adherence to seeds			
4.1.2	Drop test for packaging	ADR 3552	Yes	
	Leakproofness test	ADR 3553 or 3560	Yes	
	Internal pressure (hydraulic) test	ADR 3554	No	
	Stacking test	ADR 3555	No	
	Supplementary permeability test for drums and jerricans	ADR 3556	No	
	Approval of combination packagings	ADR 3558	Yes	
	Child resistant packaging - testing procedures for re-closable packages	ISO 8317	Yes	

Appendix 11 Part 7 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
4.1.3	Resistance of the packaging material to its contents	GIFAP Method [27]	No	
4.2	Effectiveness of cleaning procedures for application equipment and protective clothing			
4.4	Effectiveness of protective clothing and equipment under realistic conditions of use			
	Toxicity of fire effluents	ISO TR 9122	Yes	
4.6.1	Evaluation of products of neutralization (small quantities)			
	Evaluation of products of neutralization (large quantities)			
4.6.2	Pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis			GLP
4.6.3	Effectiveness of methods other than controlled incineration for disposal of plant protection products, contaminated packaging and contaminated materials			
7.1.1	Acute toxicity (oral)	EEC B.1 or B.1 bis	Yes	GLP
7.1.2	Acute toxicity (dermal)	EEC B.3	No	GLP
7.1.3	Acute toxicity (inhalation)	EEC B.2	No	GLP
7.1.4	Acute toxicity (skin irritation)	EEC B.4	No	GLP
7.1.5	Acute toxicity (eye irritation)	EEC B.5	No	GLP
7.1.6	Skin sensitization	EEC B.6	Yes	GLP

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
7.1.7	Acute toxicity (oral)	EEC B.1 or B.1 bis	Yes	GLP
	Acute toxicity (dermal)	EEC B.3	No	GLP
	Acute toxicity (inhalation)	EEC B.2	No	GLP
	Acute toxicity (skin irritation)	EEC B.4	No	GLP
	Acute toxicity (eye irritation)	EEC B.5	No	GLP
	Skin sensitization	EEC B.6	Yes	GLP
7.2.1.1	Estimates of operator exposure			
7.2.1.2	Measurement of operator exposure	Directive 88/642/EEC[28]		GLP
7.2.2	Estimate of bystander exposure			
	Measurement of bystander exposure			GLP
7.2.3.1	Estimates of worker exposure			
7.2.3.2	Measurement of worker exposure			GLP
7.3	Dermal absorption, *in vivo* in the rat			GLP
	Comparative dermal absorption, *in vitro* using rat and human skin			GLP
7.4	Toxicological data for each formulant			

[28] In so far as inhalation exposure is concerned, measuring procedures used must either comply with the reference method in the Annex to Council Directive 88/642/EEC of 16 December 1988, amending Directive 80/1107/EEC on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work, OJ No L 336, 24 December 1988, p 74, or be a method yielding equivalent results

Appendix 11 **Part 7** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies**

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
8.1	Supplementary studies on metabolism, distribution, and expression of residues in plants and livestock	Commission Guidelines [29]		GLP
8.2	Supplementary residue trials (supervised field trials)	Commission Guidelines [29]		GLP
8.3	Supplementary livestock feeding studies	Commission Guidelines [29]		GLP
8.4	Supplementary studies on the effects of industrial processing and/or household preparation (balance studies)	Commission Guidelines [29]		GLP
8.5	Supplementary residue trials in succeeding crops	Commission Guidelines [29]		GLP
8.8	Estimation of the potential and actual exposure through diet and other means	WHO Guidelines [30]		

[29] Commission document 1607/VI/97 - rev 1 of 22 July 1997, Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market

[30] Guidelines for predicting dietary intake of pesticide residues, WHO, 1989;

Application of risk analysis to food standards issues, Report of the Joint FAO/WHO Expert Consultation, Geneva, Switzerland, 13-17 March 1995 (WHO/FNU/FOS/95.3);

Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues, Report of a FAO/WHO Consultation, 1995 (WHO/FNU/FOS/95.11)

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Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
9.1.1.1	Aerobic degradation (rate) in soil	SETAC [31]	No	GLP
	Anaerobic degradation (rate) in soil	SETAC [31]	No	GLP
9.1.1.2	Soil (field) dissipation studies	SETAC [31]	No	GLP
	Soil (field) residue studies	SETAC [31]	No	GLP
	Soil (field) accumulation studies	SETAC [32]	No	GLP
9.1.2.1	Column leaching studies	SETAC [31]	Yes	GLP
9.1.2.2	Lysimeter studies	SETAC [31]	Yes	GLP
	Field leaching studies	SETAC [31]	Yes	GLP
9.1.3	Predicted environmental concentrations in soil (PEC_s)			
9.2.1	Predicted environmental concentrations in ground water (PEC_{gw})			
	Additional field testing			GLP
9.2.2	Impact on water treatment procedures			GLP
9.2.3	Predicted environmental concentrations in surface water (PEC_{sw})			
	Additional field testing			GLP
9.3	Fate and behaviour in air			GLP

[31] Procedures for assessing the environmental fate and ecotoxicity of pesticides. SETAC-Europe, 1995. ISBN number 90-5607-002-9

Appendix 11 Part 7 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
10.1	Acute toxicity exposure ratio (TER_A) for birds			
	Short-term toxicity exposure ratio (TER_{ST}) for birds			
10.1.1	Avian acute oral toxicity	SETAC [31]	No	GLP
10.1.2	Supervised cage trials			GLP
	Supervised field trials			GLP
10.1.3	Avian palatability test			GLP
10.1.4	Effects of secondary poisoning			GLP
10.2	Acute toxicity exposure ratio (TER_A) for fish, Daphnia, aquatic insect species, aquatic crustacean species and gastropod mollusc species			
	Long-term toxicity exposure ratio (TER_{LT}) for fish, Daphnia, aquatic insect species, aquatic crustacean species, gastropod mollusc species and algae			
10.2.1	Acute toxicity for fish	EEC C.1	No	GLP
	Acute toxicity for *Daphnia*	EEC C.2	No	GLP
	Algal inhibition test	EEC C.3	No	GLP
10.2.2	Microcosm or mesocosm study	SETAC-Huntingdon & EWOFT	Yes	GLP
10.2.3	Residue data in fish	SETAC-Huntingdon & EWOFT	Yes	GLP

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Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
10.2.4	Chronic (28-day) toxicity to juvenile fish			GLP
	Fish early life stage toxicity test	OECD 210	No	GLP
	Fish life cycle test			GLP
	Daphnia sp. reproduction test - 21 day	OECD 202 Part II	No	GLP
	Aquatic insect chronic toxicity/reproduction test			GLP
	Aquatic gastropod mollusc chronic toxicity/ reproduction test			GLP
10.3	Acute toxicity exposure ratio (TER_A) for terrestrial vertebrates other than birds			
	Short-term toxicity exposure ratio (TER_{ST}) for terrestrial vertebrates other than birds			
	Long-term toxicity exposure ratio (TER_{LT}) for terrestrial vertebrates other than birds			
	Acute oral toxicity			GLP
	Supervised cage trials			GLP
	Supervised field trials			GLP
	Palatability test for terrestrial vertebrates other than birds			GLP
	Effects of secondary poisoning			GLP
10.4	Hazard Quotient for bees - oral exposure (Q_{HO})			
	Hazard Quotient for bees - contact exposure (Q_{HC})			

Appendix 11 Part 7 Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
10.4.1	Bee acute oral toxicity test	EPPO 170	No	GEP-GLP [32]
	Bee acute contact toxicity test	EPPO 170	No	GEP-GLP [32]
10.4.2	Bee residue test			GEP-GLP [32]
10.4.3	Bee cage tests	EPPO 170	No	GEP-GLP [32]
10.4.4	Bee field tests	EPPO 170	No	GEP-GLP [32]
	Investigation of special effects			GEP-GLP [32]
10.4.5	Bee tunnel tests	EPPO 170	No	GEP-GLP [32]
10.5.1	Effects on non-target terrestrial arthropods using artificial substrates	SETAC-ESCORT		GEP-GLP [32]
	Effects on non-target terrestrial arthropods in extended laboratory tests	SETAC-ESCORT		GEP-GLP [32] GEP-GLP [33]
	Effects on non-target terrestrial arthropods in semi field tests	SETAC-ESCORT		
10.5.2	Effects on non-target beneficial arthropods in field tests	SETAC-ESCORT		GEP-GLP [32]
10.6.1	Acute toxicity exposure ratio (TER_A) for earthworms			
	Long term toxicity exposure ratio (TER_{LT}) for earthworms			
10.6.1.1	Earthworm acute toxicity test	OECD 207	No	GLP
10.6.1.2	Sublethal effects on earthworms			GLP

[32] At the discretion of the Member State in which they are conducted, tests started on or before 31 December 1999, to be conducted in accordance with the principles of GEP, thereafter to be conducted in accordance with the principles of GLP

Appendix 11 **Part 7** **Listing of the test guidelines specified and the requirements relating to compliance with GLP and GEP for individual Annex IIIA tests and studies**

Annex IIIA point	Description of the test or study	Guideline specified	Choice of method provided by guideline	GLP or GEP applicable
10.6.1.3	Effects on earthworms in field tests			GLP
	Residue content of earthworms			GLP
10.6.2	Effects on other soil non-target macro-organisms			GLP
	Effect on organic matter breakdown			GLP
10.7.1	Laboratory test to investigate impact on soil microbial activity	SETAC [31]	No	GLP
10.7.2	Further laboratory testing to investigate impact on soil microbial activity			GLP
	Glasshouse testing to investigate impact on soil microbial activity			GLP
	Field testing to investigate impact on soil microbial activity			GLP